Author:
Fordham, James

Title:
New Methods for the Homologation of Boronic Esters and Their Application in Synthesis

New Methods for the Homologation of Boronic Esters and Their Application in Synthesis

---

James Fordham

Supervisor: Professor Varinder K. Aggarwal FRS

A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Philosophy in the Faculty of Science.
School of Chemistry, October 2019

Abstract

The asymmetric synthesis of organic molecules is of fundamental importance to the design and preparation of new drug and agrochemical compounds. The treatment of a boronic ester with a metal carbenoid, termed a homologation reaction, is a useful strategy for accessing stereodefined boronic esters, which can participate in a plethora of transformations. This thesis reports the development of three new methods for the homologation of boronic esters and details their application towards the synthesis of complex molecules.

Firstly, enantio- and diastereopure α-sulfinyl benzoate building blocks were explored as carbenoid precursors for the homologation of boronic esters. A range of functionalised α-sulfinyl benzoates were prepared in enantioenriched form by using either a lithiation–transmetallation–trapping approach or through alkylation chemistry. These building blocks were transformed into stereodefined Mg and Li carbenoids, through sulfoxide–metal exchange, and were found to homologate boronic esters in a highly stereospecific fashion. This homologation process was rendered iterative, which allowed a molecule bearing three contiguous stereocentres to be accessed as a single stereoisomer.

Secondly, lithiated terminal epoxides were explored as reagents for the preparation of β-oxyboronic esters. Our goal was to use this transformation, in conjunction with a pre-established homologation protocol, to access polypropionate motifs, which are frequently encountered in the polyketide family of natural products. However, due to a poor reactivity profile and issues regarding the stability of β-oxyboronic esters, this strategy was abandoned.

Finally, lithiated epoxysilanes were used to achieve the vinylidene homologation of boronic esters. This reaction allowed access to a diverse range of sp^3-rich vinyl boronic esters, many of which would be difficult to prepare by other means. A divergence in mechanism was observed for some sp^2-hybridised starting boronic esters, which were found to deliver the corresponding vinyl silane products. This mechanistic divergence was probed using computation, which revealed that the reaction outcome could be rationalised by considering the stabilisation of negative charge in the transition-state of the elimination step. The vinylidene homologation reaction was applied to achieve a short and stereoselective synthesis of the proposed structure of machillene, however the NMR data of our synthetic sample did not match that which was reported. Our efforts towards the structural revision of machillene are discussed.

Contents

I. Acknowledgements……..……...……...…..iv

II. Author's declaration…….…..……..…….....v

III. Abbreviations……..…….…..……vi

1. General Introduction……..1

1.1. Substrate-Controlled Homologation of Boronic Esters…….....1

1.2. Reagent-Controlled Homologation of Boronic Esters……..4

1.2.1. Hoppe's Lithiated Carbamates…….....4

1.2.2. Lithiation–Borylation and Assembly–Line Synthesis…….……9

2. General Thesis Objectives…….…….....…14

3. α-Sulfinyl Benzoates as Precursors to Metal Carbenoids for the Stereospecific Homologation of Boronic Esters…….……....15

3.1. Introduction……...……15

3.1.1. Sulfoxide–Metal Exchange for the Synthesis of Chiral Non-Racemic Carbenoids…….……....…….15

3.1.2. Sulfoxide–Metal Exchange for the Homologation of Boronic Ester……..…….....18

3.2. Project Outline……...….21

3.3. Results & Discussion……..24

3.3.1. Notes on Collaboration…….……24

3.3.2. Synthesis of Enantioenriched α-Sulfinyl Benzoates…….….24

3.3.2.1. Preparation *via* Lithiation–Transmetallation–Trapping…….....24

3.3.2.2. Preparation *via* Alkylation…….……...27

3.3.3. Homologation of Boronic Esters with Carbenoids Derived from Enantioenriched α-Sulfinyl Benzoates…….….36

3.3.3.1. Reaction Optimisation……..……36

3.3.3.2. Substrate Scope……...….38
3.3.3.3. Iterative Homologation Sequence……....42
3.4. Conclusions……45
4. Lithiated Epoxides for the Introduction of Hydroxyl Groups into Assembly–Line Synthesis……46
4.1. Introduction……....46
4.1.1.Preparationand Transformations of Stabilised Lithiated Epoxides…….46
4.1.2. Preparation and Transformations of non-Stabilised Lithiated Epoxides…….49
4.2. Project Outline……..……..54
4.3. Results & Discussion……..57
4.3.1. Reaction Optimisation…….....57
4.3.2. Iterative Study Towards Polypropionate Motif **270**……..64
4.4. Conclusions……..…….69
5. Vinylidene Homologation of Boronic Esters and its Application to the Synthesis and Structural Revision of Machillene……...……70
5.1. Introduction……..……..70
5.1.1. Vinyl Boronic Esters as Versatile Synthetic Intermediate…….70
5.1.2. Methods for the Preparation of Vinyl Boronic Esters…….....80
5.2. Project Outline……86
5.3. Results & Discussion…….....90
5.3.1. Notes on Collaboration…….....90
5.3.2. Vinylidene Homologation of Boronic Esters …….……...90
5.3.3. Total Synthesis of the Proposed Structure of Machillene…….99
5.3.4. Structural Reassignment of Machillene and Synthesis of Revised Structure **523a**…….....111
5.4. Conclusions and Outlook…….…….126
6. General Conclusion……...……130
7. Experimental…….……132

7.1. General Information……132
7.2. Materials & Reagents……..……..……...132
7.3. α-Sulfinyl Benzoates as Carbenoid Precursors for the Homologation of Boronic Esters……..……..…….134
7.3.1. General Procedures……..134
7.3.2. Preparation of Individual Compounds…….……138
7.4. Lithiated Epoxides for the Introduction of Hydroxyl Groups into Assembly–Line Synthesis……..……..…….....169
7.4.1. General Procedures……..169
7.4.2. Preparation of Individual Compounds…….……170
7.5. Vinylidene Homologation of Boronic Esters and its Application to the Synthesis and Structural Revision of Machillene……182
7.5.1. General Procedures……..182
7.5.2. Preparation of Individual Compounds…….183
8. References ……..……..243

I. Acknowledgements

First and foremost, I would like to thank Prof. Varinder Aggarwal for the opportunity to work in his amazing research group and for the invaluable assistance and guidance he has afforded me throughout my PhD.

I am very grateful to our research officers, Dr. Eddie Myers and Dr. Adam Noble, for the many stimulating discussions that we shared.

I am lucky to have worked with some excellent scientists throughout my studies. In particular, I thank Giorgia and Murat for welcoming me into the sulfoxide team and for the support they gave me at the start of my PhD. I thank Rory, my automation brother, together we have endured every possible emotion during our exploits in Basel and in the instrument room. Thank you to Valerio who, in my absence, is charged with caring for not only Maximus (the Chemspeed), but also Rory. Thank you to my collaborators Dr. Matt Grayson, Prof. Craig Butts and Oliver Dutton, for their computational expertise. Thank you to the many support staff at the department of chemistry, without whom this thesis would not be possible.

During my 4 years I have made many friends who in turn have made my PhD a very enjoyable experience. I cannot name everyone here, so will thank just a few (not listed above): Lydia, Dabs, Louise & Jon (CDT family), Joe (unknown person from Nottingham days turned housemate), Stevie & Felix (gin connoisseurs and Merck retro legends), Beatrice, Roly & Daniel (lab neighbours and pools of knowledge), Tong (lithiation–borylation master/teacher and excellent host), Dabao (poor choice in street food), Charlotte, Riccardo & Jason (running club).

II. Author’s declaration

“I declare that the work in this dissertation was carried out in accordance with the Regulations of the University of Bristol. The work is original, except where indicated by special reference in the text, and no part of the dissertation has been submitted for any other academic award. Any views expressed in the dissertation are those of the author.”

SIGNED: …….. DATE: …….

III. Abbreviations

The ACS standard List of Abbreviations, found within the ‘ACS Guidelines For Authors’, was used with the following additions:

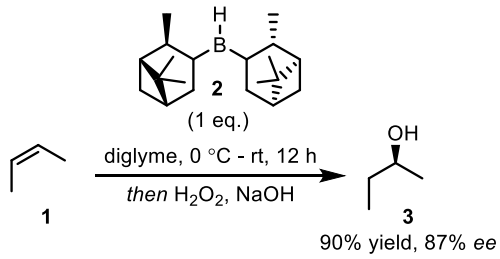
α_C	α-carbon
α_H	α-proton
β_n	bite angle
Δδ	chemical shift difference
μwave	microwave
AIBN	azobisisobutyronitrile
APCI	Atmospheric Pressure Chemical Ionisation
avg	average
Bcat	catechol boronic ester
Bneo	neopentyl boronic ester
Bpin	pinacol boronic ester
Cb	diisopropyl carbamate
DMA	*N*,*N*-dimethylacetamide
DMAP	*N*,*N*-dimethylaminopyridine
DMM	dimethoxymethane
DMP	Dess-Martin periodinane
dpmd	1,3-dimethylpentane-1,3-diol
DPPA	diphenylphosphoryl azide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,2-bis(diphenylphosphino)ferrocene
ent	enantiomeric
eq.	equivalents
e.r.	enantiomeric ratio
e.s.	enantiospecificity
HBcat	catechol borane
HBpin	pinacol borane

HKR	hydrolytic kinetic resolution
LDA	lithium diisopropylamide
*m*CPBA	*meta*-chloroperbenzoic acid
MM	molecular mechanics
NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
OTf	trifluoromethanesulfonate
oxone	potassium peroxymonosulphate
PMA	phosphomolybdic acid
PMHS	polymethylhydroxysilane
rt	room temperature
SE’	electrophilic substitution with allylic rearrangement
SE'_{inv}	electrophilic substitution with stereoinvertive allylic rearrangement
sp	sparteine
TBME	^{t}butyl methyl ether
TESOTf	triethylsilyl trifluoromethanesulfonate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TIB	2,4,6-triisopropyl benzoate
TIBOH	2,4,6-triisopropyl benzoic acid
TMEDA	*N,N,N’,N’*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TSs	transition-states
TTMSS	tris(trimethylsilyl)silane

1. General Introduction

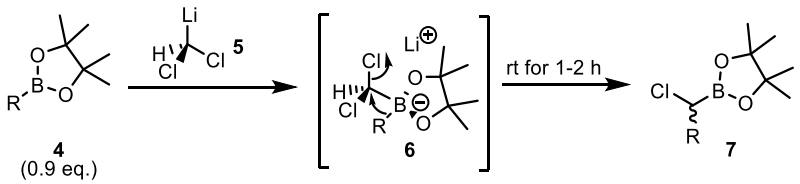
1.1. Substrate-Controlled Homologation of Boronic Esters

It has long been established that organoboron compounds are useful intermediates in organic synthesis.[1-2] Indeed, the first non-enzymatic highly enantioselective transformation involved the hydroboration of disubstituted alkene **1** with diisopinocamphenylborane (**2**) which, after oxidation, gave alcohol **3** with unprecedented levels of enantioinduction (Scheme 1).[3-4] Since this pioneering work, innumerable contributions to the field have been made and organoboron compounds can now be efficiently converted into many functional groups with excellent stereospecificity.[5-7]



Scheme 1. Enantioselective hydroboration of alkene **1**

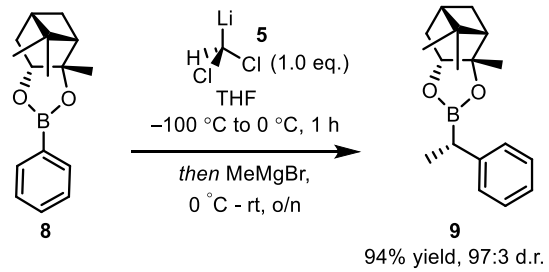
In 1980, Matteson and co-workers described a powerful method that enabled the chain-extension of boronic esters, whilst simultaneously providing a means for further functionalisation.[8] This homologation protocol involved initial attack of lithium carbenoid **5** on the empty p-orbital of boron to give boronate complex **6** (Scheme 2). Carbenoid **5** was prepared *in-situ* by deprotonation of CH_2Cl_2 with lithium diisopropylamide (LDA) in dimethoxyethane (DME) at –78 °C,[9] or *ex-situ via* deprotonation of CH_2Cl_2 with *n*-butyl lithium in tetrahydrofuran (THF) at –100 °C.[10] Upon warming, **6** underwent a stereospecific 1,2-migration to form α-chloro boronic ester **7**, which was reacted with many nucleophiles to give synthetically valuable products.[11]



Scheme 2. Homologation of boronic ester **4** with carbenoid **5**

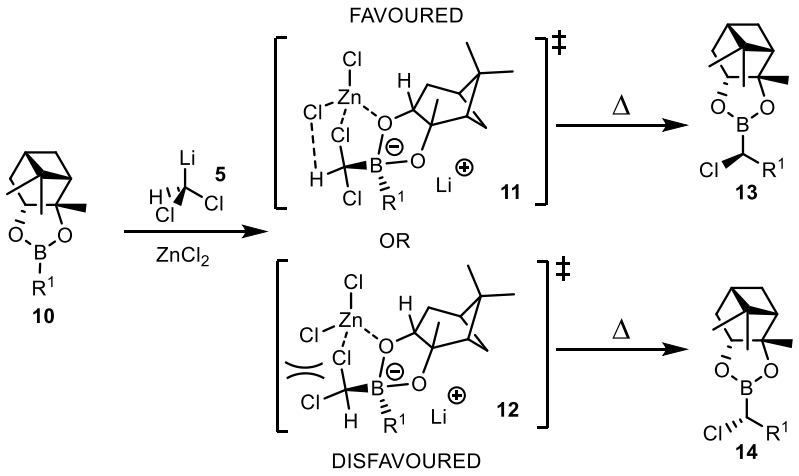
For the 1,2-metallate rearrangement to occur, the C–B bond of boronate complex **6** must adopt an anti-periplanar relationship with respect to the leaving group, thus maximising overlap of the C–B σ-orbital with the C–Cl σ*-orbital.[12] The migration proceeds in a concerted fashion and results in inversion of configuration at the migratory terminus. Therefore, any stereochemical information in the starting boronic ester is transferred to the product.

Matteson and co-workers utilised this inherent property to develop a substrate-controlled approach for the homologation of boronic esters.[13-14] By employing a chiral non-racemic diol as the ligand on boron, they found that homologation with carbenoid **5** followed by reaction with methyl magnesium bromide gave the corresponding products with high diastereoselectivity (Scheme 3); which was determined by optical rotation measurements of the corresponding alcohols obtained after oxidation.



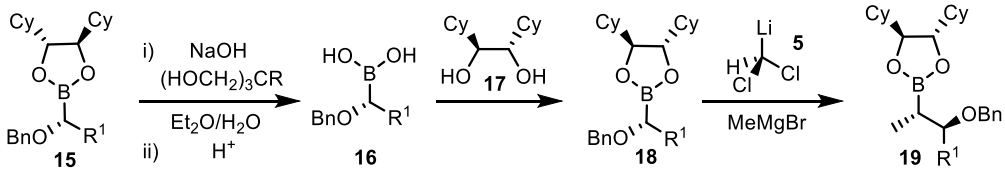
Scheme 3. Substrate-controlled homologation of boronic esters

However, for some substrates reactions were poorly selective and low yielding.[15] Studies later revealed that exposure of the intermediate α-chloro boronic ester to lithium chloride resulted in epimerisation at the carbon centre, which was used to rationalise the observed variation in diastereomeric ratio.[16] These results prompted the authors to investigate the effect of the addition of chloride complexing agents to the reaction. It was found that addition of sub-stoichiometric $ZnCl_2$ greatly enhanced stereoselectivity and, in some cases, yield.[17] Corey and co-workers proposed a model to account for these observed improvements (Scheme 4).[18] It was suggested that diastereomer **13** is formed preferentially due to the presence of a stabilising hydrogen bond interaction in transition state **11**, which is not possible for opposing transition state **12** that leads to diastereomer **14**.



Scheme 4. Transition-state analysis for a diastereoselective homologation in the presence of $ZnCl_2$

The Matteson homologation has found many notable applications including preparation of homoallylic alcohols and amino acids, and in the field of natural product synthesis.[19-21] Whilst this work undoubtedly demonstrates the power of organoboron chemistry for asymmetric synthesis, it does suffer from significant drawbacks. Namely, the stereochemical outcome of the reaction is dictated by the chiral diol on boron and is thus under substrate control. Therefore, if a desired stereoisomer in a homologation sequence is of opposite configuration, the stereochemistry of the ligand must be inverted (Scheme 5). This is not only limiting in that an additional two steps are required to interconvert the ligands, but also because these transesterification reactions are known to be sluggish and often low yielding.[22]

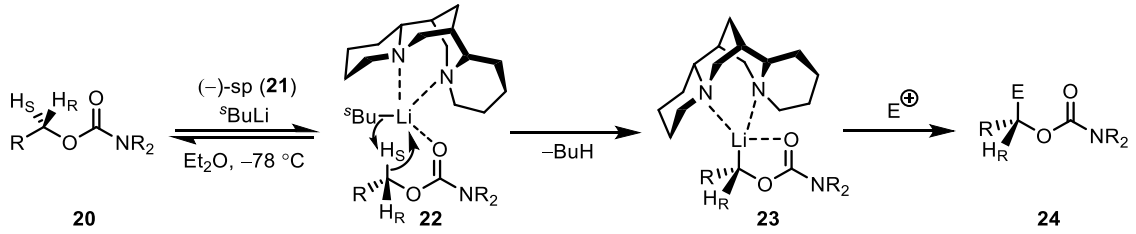


Scheme 5. A representative transesterification–homologation process

1.2. Reagent-Controlled Homologation of Boronic Esters

1.2.1. *Hoppe's Lithiated Carbamates*

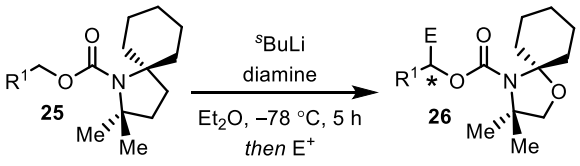
A more attractive prospect for asymmetric synthesis involves a reagent-controlled approach. In such a process, the stereochemical outcome of a reaction is determined by a reagent, not the starting material. Therefore, providing that both enantiomeric (*ent*) forms of the chiral reagent are accessible and the substrate partner does not influence the stereo-defining step, either stereoisomer of the desired product should be equally obtainable. This concept is aptly demonstrated by considering the preparation and reactions of Hoppe's lithiated carbamates (Scheme 6).[6]



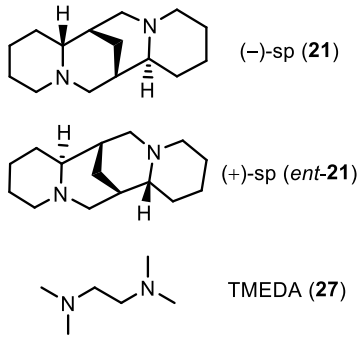
Scheme 6. Asymmetric deprotonation of carbamate **20** and subsequent trapping with an electrophile

In 1990, Hoppe and co-workers first reported that prochiral primary alkyl carbamates **20** could be stereoselectively deprotonated at low temperature with *s*-butyl lithium in the presence of stoichiometric amounts of the chiral diamine (–)-sparteine (sp) (**21**).[23] The lithium atom of ^{s}BuLi is first complexed by the diamine and the oxygen of the carbamate carbonyl to form pre-lithiation complex **22**. Due to the steric environment created by (–)-sp (**21**), the carbamate is stereoselectively deprotonated to give chiral non-racemic lithiated carbamate **23**. Due to co-ordination of (–)-sp (**21**) to the lithium cation, complex **23** is rendered configurationally stable and has generally been shown to react with electrophiles with high stereofidelity (Table 1). It is noteworthy that in the overall process, the carbamate is acting both as a directing group, which enables formation of the pre-lithiation complex, and a weak electron-withdrawing group, which facilitates deprotonation.[24] The selectivity of the asymmetric deprotonation reaction has since been rationalised using density functional theory (DFT), which revealed that deprotonation of the *pro*-(*S*) hydrogen atom was favoured over the *pro*-(*R*) hydrogen atom by 2.75 kcal/mol.[25]

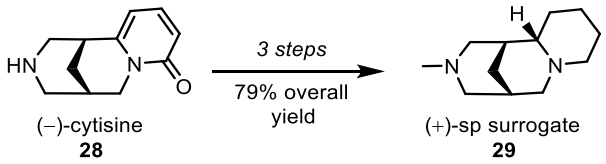
Table 1. Lithiation of primary carbamates with electrophilic trapping



R^1	diamine	E^+	yield (%)	ee (%)
Me	TMEDA	CO_2	60	0
Me	(–)-sp	CO_2	75	>95
Me	(–)-sp	Me_3SnCl	76	>95
^{n}Hex	(–)-sp	MeI	81	>95

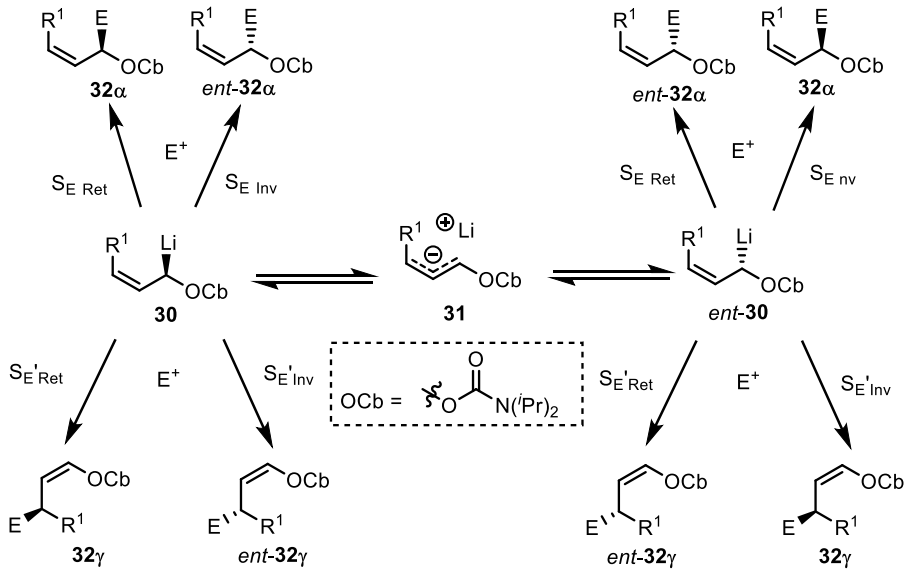


As stated earlier, a reagent-controlled approach to asymmetric synthesis requires that both enantiomers of a chiral reagent are available. For a long time, this was not the case and whilst (–)-sp (**21**) could be easily accessed, (+)-sp (*ent*-**21**) was not available. This sudden shortage inspired O'Brien and co-workers to design a (+)-sp surrogate (**29**), which could be prepared from the alkaloid cytisine **28** (Scheme 7).[26]



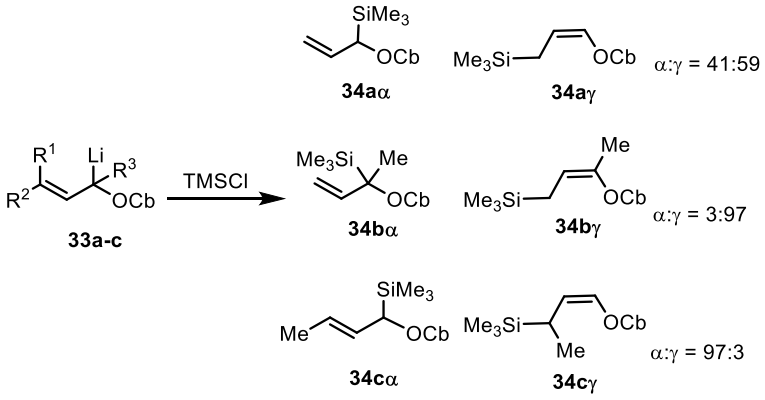
Scheme 7. Preparation of (+)-sp surrogate (**29**)

The lithiated carbamate approach is not limited to simple aliphatic substrates - extensive studies by Hoppe has shown that allylic systems can also be employed.[27] For these carbenoid species, several issues had to be considered. Firstly, the allyl system increases the stability of the carbanion by resonance, and therefore promotes formation of a solvent separated ion-pair **31** (Scheme 8).[28] This stabilisation facilitates inversion at the carbon centre and thus increases the likelihood of racemisation. There is also the possibility that the carbenoid reacts with electrophiles at the γ-position *via* electrophilic allylic substitution (S_E'), which could lead to product mixtures containing two regioisomers. Furthermore, reactions with electrophiles can proceed with inversion and/or retention of stereochemistry, potentially leading to enantiomeric mixtures of product.



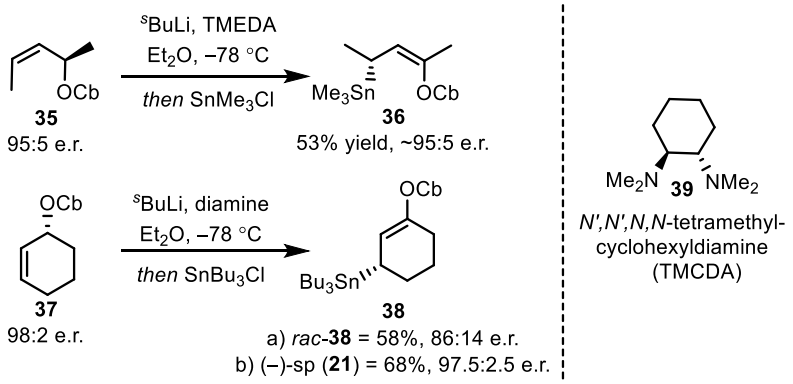
Scheme 8. Possible regio- and stereochemical outcomes of electrophilic trapping of **30**

Hoppe demonstrated that a range of allylic carbamates could be lithiated in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA, **27**).[29] The regioselective outcome of the reaction of these carbenoids with electrophiles proved to be highly substrate dependent (Scheme 9).[30] Whilst lithiated primary unsubstituted allylic carbamate **33a** was trapped with chlorotrimethylsilane (TMSCl) with poor regioselectivity, primary γ-substituted allylic carbamate **33b** reacted almost exclusively at the α-position. Conversely, secondary α-substituted carbamate **33c** reacted selectively at the γ-position. The observed selectivity was attributed to the relative steric hindrance of the two positions. Due to the beneficial co-ordination from the carbonyl of the carbamate, the lithium cation resides exclusively at the α-position of the lithiated species.[31] Therefore when considering the relative hindrance of the α/γ positions, one must account for the steric environment imparted by the diamine.[32]



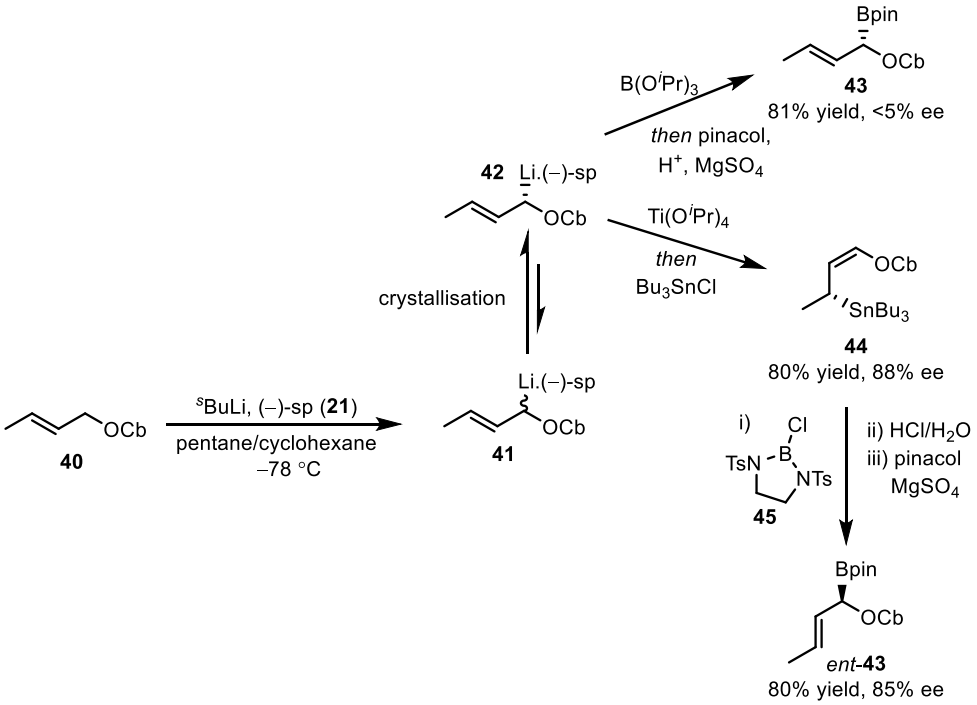
Scheme 9. Trapping of allylic carbamates **33a-c** with TMSCl

The configurational stability of allylic carbamates was also found to be substrate dependent. Hoppe demonstrated that enantioenriched allylic carbamate **35** could be lithiated in the presence of TMEDA (**27**) and trapped with trimethyltin chloride to give γ-stannylated compound **36** with complete inversion of stereochemistry (Scheme 10).[33] This revealed that lithiated carbamates of this type are configurationally stable and react with $SnMe_3Cl$ *via* a stereoinvertive electrophilic substitution mechanism ($S_E'_{inv}$). However, when chiral non-racemic cyclohexenyl carbamate **37** was lithiated under similar conditions and subsequently treated with tributyltin chloride, the stannylated product was obtained with lower levels of enantiospecificity (e.s.).[34] In this instance, the stereoselectivity could be improved with bulkier diamines, such as (–)-sp (**21**).



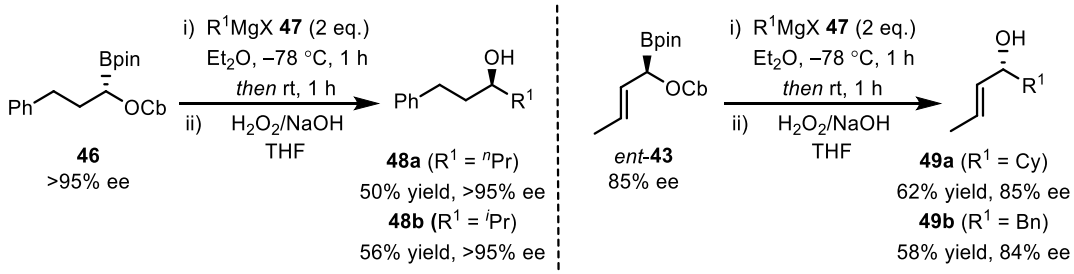
Scheme 10. Substrate dependent configurational stability of lithiated allylic carbamates

Hoppe showed that lithiated allylic carbamate **41** was configurationally labile but could be enriched *via* dynamic thermodynamic resolution to form crystalline complex **42** as a single diastereomer (Scheme 11).[35] However, upon reaction with triisopropoxy borate and after transesterification, boronic ester **43** was isolated as a racemic (*rac*) mixture.[36] This was because $B(O^iPr)_3$ was not intercepted by crystalline **42**, and only reacted with the configurationally unstable carbenoid **41** in solution. This low selectivity was overcome by transmetallation and trapping to form stannane **44**, which could be converted to boronic ester *ent*-**43** with high enantiospecificity.



Scheme 11. Enantioselective synthesis of allylic boronic ester *ent*-**43**

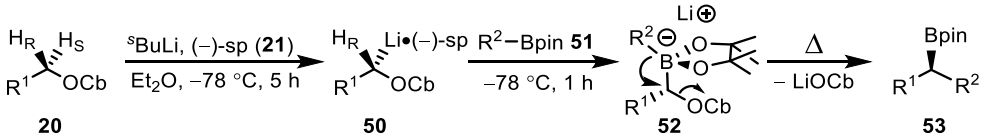
Subsequently, it was shown that both secondary and allylic boronic esters **46** and *ent*-**43** reacted with Grignard reagents **47** with high enantiospecificity (Scheme 12).[37] Importantly, if the product bearing the opposite configuration was desired, one could access it by the same method by employing (+)-sp (*ent*-**21**) to synthesise starting boronic esters *ent*-**46** and **43**. Thus, this process meets the requirements of a reagent-controlled approach towards the homologation of boronic esters. Significantly, Kocienski and co-workers had previously identified that carbamates act as a proficient nucelofugal group in the 1,2-metallate rearrangement of organocuprates.[38]



Scheme 12. Reaction of boronic esters **46** and *ent*-**43** with Grignard reagents

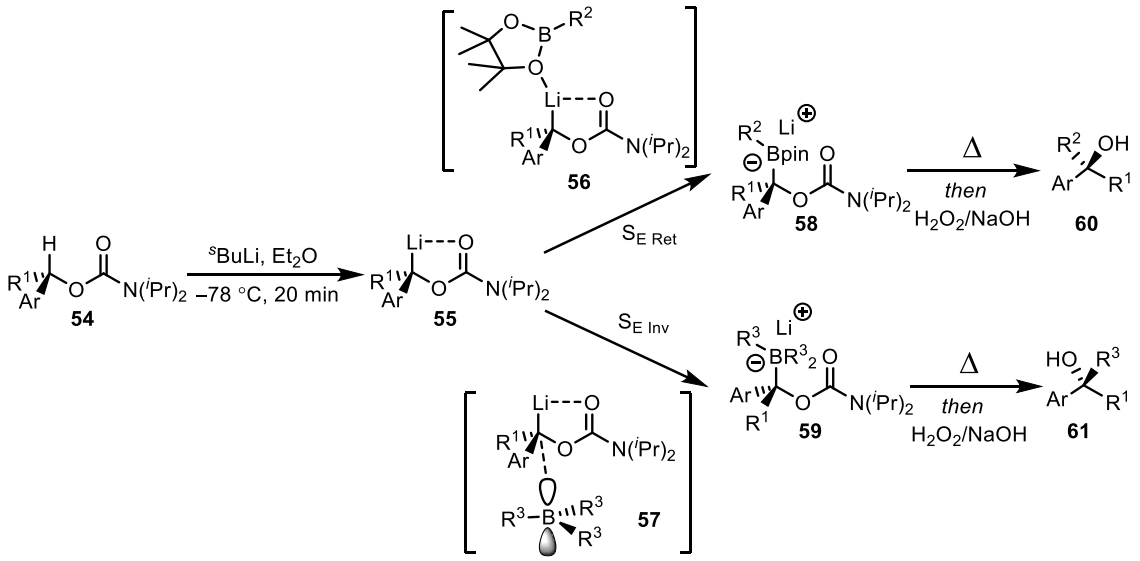
1.2.2. *Lithiation–Borylation & Assembly–Line Synthesis*

Hoppe's stepwise, reagent controlled approach to the asymmetric homologation of boronic esters has been adapted by Aggarwal and co-workers,[39-40] and by Kocienski in a single report.[41] It was shown that chiral non-racemic lithiated carbamate **50** could be reacted directly with boronic ester **51** to form boronate complex **52**. After warming, boronate **52** underwent 1,2-metallate rearrangement to give enantioenriched boronic ester **53** (Scheme 13). This modification, coined lithiation–borylation, enabled the transformation described by Hoppe to be performed in a single step, rendering it more suited to iterative synthesis.



Scheme 13. One-pot and reagent-controlled homologation of boronic ester **51**

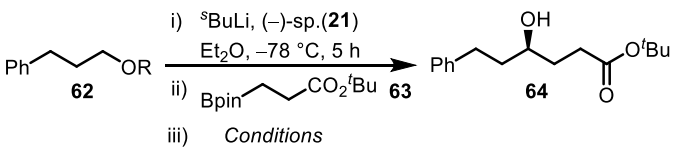
A limitation of Matteson's procedure was that, due to diminished levels of diastereoselectivity, it could not be used to synthesise tertiary boronic esters.[42] Aggarwal and co-workers demonstrated that their methodology could be extended to secondary lithiated carbamates, which were found to be trapped by boranes and boronic esters to give tertiary products.[43] Notably, depending on the boron source, the alcohols obtained following oxidation were found to be of opposing configuration, which was attributed to the operation of two different mechanisms (Scheme 14). For pinacol boronic esters (Bpin), it was proposed that the oxygen of the diol ligand co-ordinates to the lithium cation, which directs the electrophiles approach along the top-face, and thus led to retention of stereochemistry upon trapping. In contrast, for boranes, there is no favourable interaction between the incoming electrophile and the lithiated species and therefore approach occurs from the less hindered bottom face.



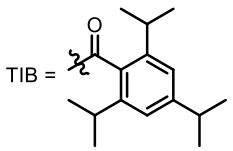
Scheme 14. Enantiodivergent synthesis of tertiary alcohols

Aggarwal and co-workers later found that, for some reactions between lithiated carbamates and boronic esters, the 1,2-metallate rearrangement was sluggish and, even upon heating to elevated temperatures, could not be instigated (Table 2).[44] In some cases this issue could be overcome by addition of stoichiometric amounts of a Lewis acid, typically $MgBr_2$. However, the need for Lewis acid additives could be mitigated by using 2,4,6-triisopropylbenzoate (TIB) esters as a carbamate substitute.[44] The lithiated benzoates could be prepared *via* an analogous asymmetric lithiation procedure, and were found to undergo 1,2-metallate rearrangement more readily than the corresponding carbamates. This method was extended to the synthesis of a wider range of boronic esters and delivered the homologated products in comparable levels of enantioselectivity to the carbamates.

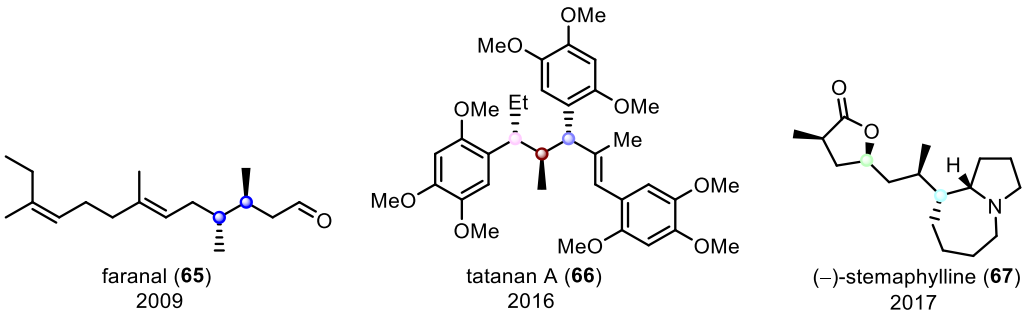
Table 2. TIB esters as carbamate replacements



Entry	R	Conditions	Yield (%)	e.r.
1	Cb	16 h, reflux	0	N/A
2	Cb	$MgBr_2$•Et_2O (2 eq.), 5 d , reflux	35	93:7
3	TIB	16 h, reflux	63	96:4

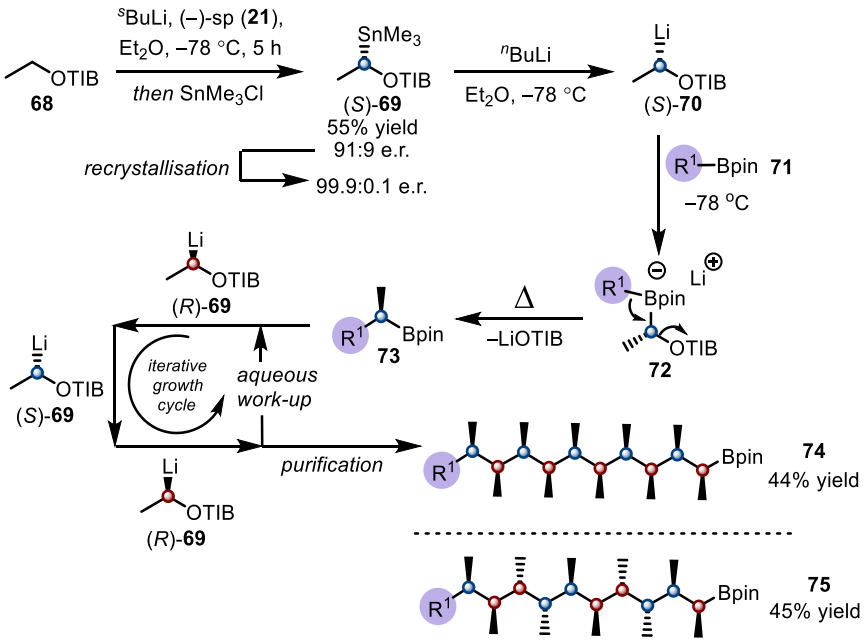


The methodologies described above have subsequently been applied to the synthesis of numerous natural products, often by employing iterative homologation reactions to install contiguous stereocentres (Scheme 15).[45-47]



Scheme 15. Natural products synthesised by lithiation–borylation; the stereocentres set by asymmetric lithiation have been highlighted

One of the most useful methods to arise from the lithiation–borylation era was the realisation that enantioenriched stannanes, (*R*)-**69** and (*S*)-**69**, could be employed as precursors to chiral carbenoids (Scheme 16).[48] Stannanes (*R*)-**69** and (*S*)-**69** were prepared by enantioselective lithiation of TIB ester **68** with (+)-sp (*ent*-**21**) and (–)-sp (**21**) respectively, followed by trapping with $SnMe_3Cl$ and, after recrystallisation, were isolated in enantiopure form. Upon treatment with ^{n}BuLi at –78 °C, stereoretentive tin–lithium exchange revealed the lithiated species. (*S*)-**70** was trapped with boronic ester **71** to form the corresponding boronate complex **72**, which, upon warming, underwent 1,2-metallate rearrangement. Filtration of the crude reaction mixture removed the insoluble lithium triisopropylbenzoate by-product to give crude boronic ester **73**. Owing to the efficiency of the process, the crude homologated product could be used directly in subsequent reactions, without the need for chromatographic purification. This enabled a further nine homologations to be performed with only an aqueous work-up required after every three homologations and, after a single purification procedure, boronic ester **74** was isolated as a single stereoisomer. By alternating the enantiomer of **69**, any diastereomer of **74** could theoretically be accessed and this was demonstrated, in part, by the synthesis of boronic ester **75**.

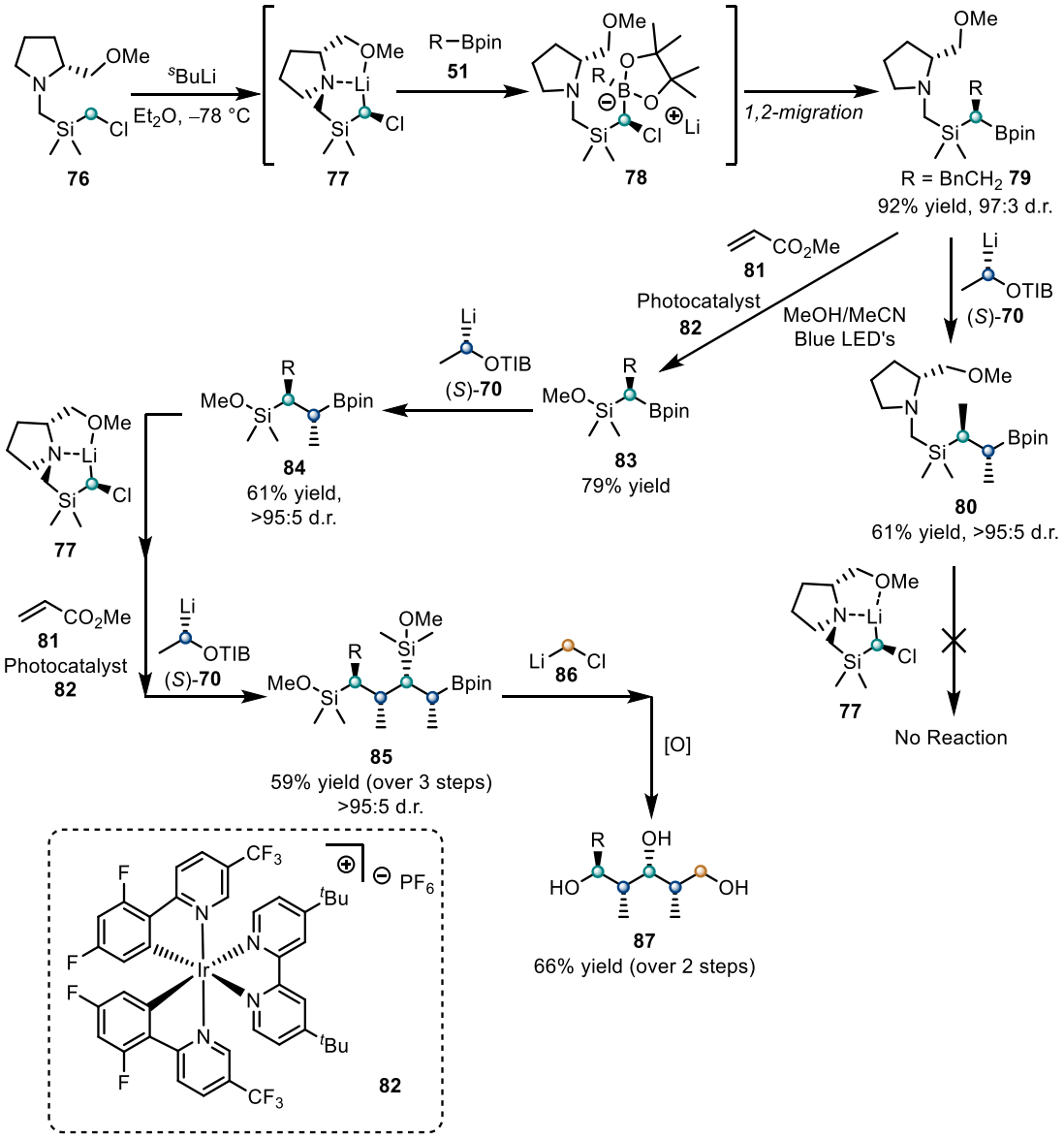


Scheme 16. Assembly–line synthesis

For an iterative process such as this to be efficient, a number of criteria must be met; firstly, the carbenoid must be generated in enantiopure form (>99:1 e.r.) and be configurationally stable under the reaction conditions, so as to avoid the formation of diastereomeric mixtures that would lead to purification difficulties. Secondly, the carbenoid must react irreversibly with a boronic ester (limiting reagent) in an efficient process so as to avoid any under-homologation. Thirdly, 1,2-metallate rearrangement of the boronate complex should only begin to occur at a stage where the carbenoid is no longer chemically stable, thus circumventing any possibility of over-homologation.

Assembly–line synthesis has recently been applied to the synthesis of polypropionate motifs (Scheme 17).[49] The authors found that lithiated α-chlorosilane **77** could be generated as a single diastereomer upon treatment of **76** with ^{s}BuLi at low temperature. Subsequent trapping with a boronic ester lead to the formation of boronate **78** which, following 1,2-migration, furnished homologated compound **79** in high yield and diastereoselectivity. Boronic ester **79** could be homologated with carbenoid (*S*)-**70** with good efficiency, however efforts to homologate further with **77** were met with failure, which was attributed to reduced electrophilicity at the boron centre owing to donation from the nitrogen atom lone pair. It was found that the pyrrolidine 'side-arm' could be cleaved through photoredox catalysis and subjection of the resulting product **83** to homologation with carbenoid (*S*)-**70** gave product **84** in excellent yield and

diastereoselectivity. By performing this sequence iteratively, polypropionate motifs such as **87** could be accessed after a global oxidation procedure. This iterative strategy gave access to all diastereomers of **87** with near-perfect levels of stereocontrol, further demonstrating the power of assembly–line synthesis.



Scheme 17. Assembly–line synthesis for the preparation of polypropionate motifs

2. General Thesis Objectives

Firstly, this thesis will address the limitations of the assembly–line methodology outlined in Scheme 16 (page 12). We will explore the use of α-sulfinyl benzoates as carbenoid precursors for the homologation of boronic esters, as replacements for α-stannyl benzoates, such as (*S*)-**69**. We anticipate that we will be able to prepare enantiopure α-sulfinyl benzoates without the need for the expensive chiral diamines, which would offer a significant advantage over the organotin chemistry. Moreover, the low toxicity of sulfoxides relative to stannanes makes this new homologation protocol much safer and hopefully more attractive to the wider scientific community.

Next, we will look to address the shortcomings of the lithiated α-chlorosilane approach to polypropionate motifs (Scheme 17, page 13). Whilst an elegant methodology, the homologation of boronic esters with lithiated α-chlorosilanes does not proceed in high yield when the organoboron is sterically hindered. In addition, the need to cleave the pyrrolidine sidearm after every homologation raises the step count of the process dramatically. We hope that the use of a less hindered nucleophile, a lithiated epoxide, will lead to a more efficient reaction with hindered boronic esters. Furthermore, we envisage a strategy to polypropionate motifs that does not require an additional manipulation after each homologation with our lithiated epoxide building block.

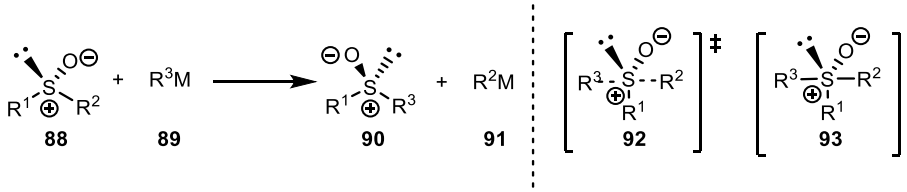
Finally, the homologation of boronic esters into vinyl boronic esters will be investigated. This transformation is attractive, as vinyl boronic esters are versatile intermediates that can undergo a wide range of transformations. Furthermore, recent developments in the preparation of aliphatic boronic esters means that a vinylidene homologation protocol would enable the synthesis of novel vinyl boronic esters, that would be otherwise difficult to access.

3. α-Sulfinyl Benzoates as Precursors to Metal Carbenoids for the Stereospecific Homologation of Boronic Esters

3.1. Introduction

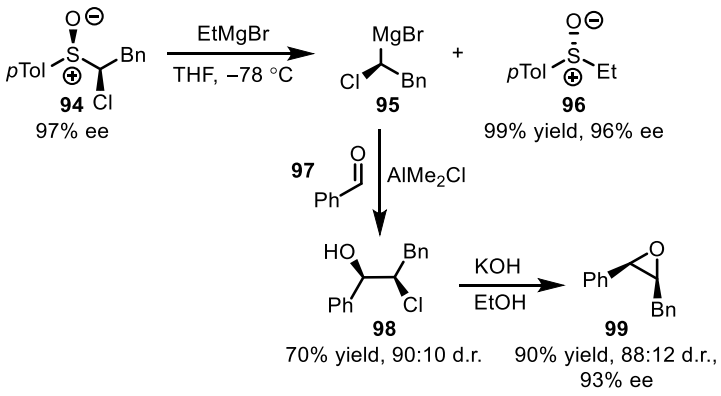
3.1.1. *Sulfoxide–Metal Exchange for the Synthesis of Chiral Non-Racemic Carbenoids*

The sulfoxide–metal exchange reaction has long been recognised as a route to optically pure dialkyl sulfoxides.[50] Upon treatment of sulfoxide **88** with organometallic **89**, typically an organolithium or Grignard reagent, a ligand exchange process occurs, which leads to formation of sulfoxide **90** and organometallic species **91** (Scheme 18).[51] The driving force for the reaction is the stability of the newly-generated carbanion, as the ligand that leaves is of lowest pK_a and therefore best able to stabilise a negative charge.[52] The transformation itself is stereospecific and proceeds with inversion of configuration at sulfur; two mechanisms have been proposed to account for this observation.[53] The first involves a nucleophilic substitution reaction (S_N2) that proceeds *via* pentacoordinate transition state **92**, the second proceeds *via* pentavalent intermediate **93**. Notably, for the latter pathway to be plausible, Berry *pseudo*-rotation must be restricted otherwise a racemic product would be expected, which is not observed experimentally.[54-55]



Scheme 18. Sulfoxide–metal exchange

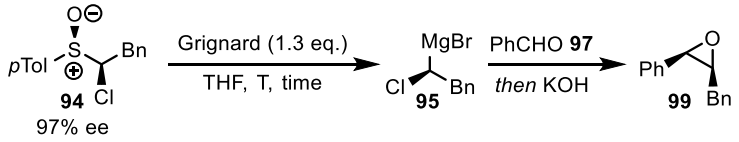
Hoffman and co-workers described that enantioenriched sulfoxides could be employed as precursors to chiral non-racemic carbenoids.[56] They reported that enantioenriched α-chlorosulfoxide **94** underwent an exchange reaction with EtMgBr to generate carbenoid **95** and dialkyl sulfoxide **96**, which was isolated in high yield and with almost complete enantiospecificity (Scheme 19). Importantly, they demonstrated that carbenoid **95** was configurationally stable at –78 °C. Upon trapping of **95** with benzaldehyde (**97**) and subsequent ring-closing, epoxide **99** was obtained with high optical purity.



Scheme 19. Sulfoxide-metal exchange for the generation of chiral non-racemic carbenoids

The degree of carbenoid racemisation was found to be highly dependent on both the Grignard reagent and the reaction temperature (Table 3).[57] Whilst the carbenoid derived from exchange with EtMgBr exhibited significant racemisation at –50 °C after just 15 minutes (Entry 2), the same organometallic generated from diisopropyl magnesium, demonstrated synthetically useful levels of configurational stability under the reaction conditions, even at –20 °C (Entry 5). This report also described that addition of stoichiometric amounts of magnesium dihalide salts (Entries 6 and 7) reduced the stereospecificity of the reaction. Here, the racemisation process was tentatively assigned to an S_N2 halide-exchange mechanism.[58]

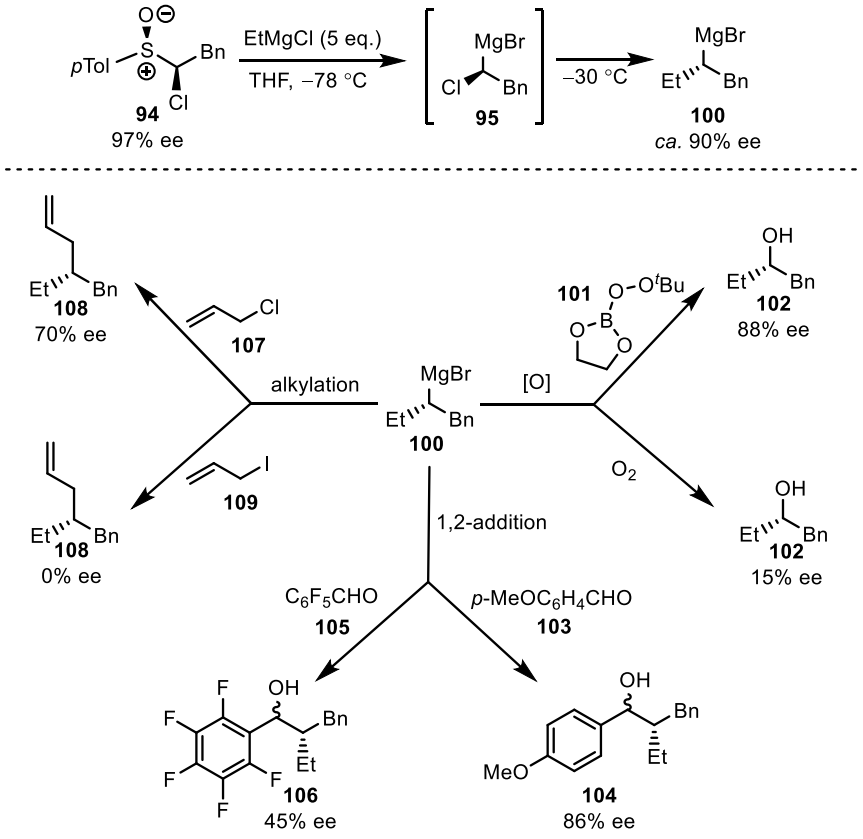
Table 3. Effect of different Grignard reagents, temperature and additives on the yield and enantiopurity of epoxide **99**



Entry	Grignard reagent	T (°C)	Time (min)	Yield (%)	ee (%)
1	EtMgBr	–50	5	71	91
2	EtMgBr	–50	15	70	64
3	EtMgBr	–50	20	70	60
4	$^{i}Pr_2Mg$	–50	15	83	92
5	$^{i}Pr_2Mg$	–20	15	48	91
6	$^{i}Pr_2Mg$ + $MgBr_2$ (1 eq.)	–50	15	84	88
7	$^{i}Pr_2Mg$ + MgI_2 (1 eq.)	–50	15	60	15

Hoffman and co-workers were keen to investigate whether a chiral Grignard reagent might be used to differentiate between polar and radical reactions (Scheme 20).[59] In order to probe this, α-chlorosulfoxide **94** was treated with an excess of EtMgCl to generate the α-chloro magnesiated species **95**, which was converted to Grignard **100** after

reaction with a second equivalent (eq.) of EtMgCl. The enantiopurity of Grignard **100** was determined independently through trapping experiments and the organometallic was then subject to a range of transformations. Firstly, oxidation with 2-(*tert*-butylperoxy)-1,3,2-dioxaborolane (**101**) gave product **102** with excellent stereospecificity, indicative of a polar pathway.[60] Conversely, reaction of **100** with molecular oxygen gave **102** with significantly reduced enantiopurity, consistent with a predominantly radical process. The addition of **100** into aldehydes was then investigated.[61] Reaction with 4-methoxybenzaldehyde (**103**) gave enantioenriched material, whereas addition into pentafluorobenzaldehyde (**105**) gave product **106** in just 45% ee. The reduced stereospecificity was attributed to competing polar and radical pathways. Contrasting mechanisms were also proposed for alkylation. While alkylation with allyl chloride **107** gave **108** with only slightly reduced optical purity, the reaction with allyl iodide **109** gave **108** as a racemate, consistent with an exclusively radical process.

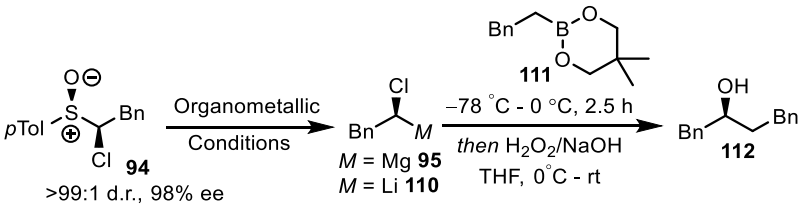


Scheme 20. Preparation and reactivity of chiral non-racemic Grignard reagent **100**

3.1.2. *Sulfoxide–Metal Exchange for the Homologation of Boronic Esters*

Blakemore and co-workers have previously described that chiral non-racemic carbenoids derived from sulfoxide–metal exchange can be harnessed for the homologation of boronic esters (Table 4).[62] They found that when magnesium carbenoid **95** was generated *ex-situ*, by treatment of α-chlorosulfoxide **94** with EtMgCl in CH_2Cl_2 at –78 °C, and subsequently exposed to neopentyl boronic ester (Bneo) **111**, after oxidation, the corresponding alcohol **112** was isolated in low yield and moderate enantiopurity (Entry 1). The poor reaction success was attributed to the chemical lability of **95** under the reaction conditions. This initial result was greatly improved upon by employing the more reactive lithium carbenoid **110**, which was generated *in-situ* by the treatment of sulfoxide **94** with ^{n}BuLi in the presence of boronic ester **111**. This modification gave alcohol **112** in high yield and with almost complete enantiospecificity (Entry 2). Notably, when the same transformation was attempted by forming lithium carbenoid **110** under *ex-situ* conditions, no product was obtained (Entry 3). The poor performance of lithium carbenoid **110** under *ex-situ* conditions relative to magnesium carbenoid **95** is reflective of the greater chemical instability of the α-chlorolithium species, when compared to the corresponding Grignard reagent.[63-65]

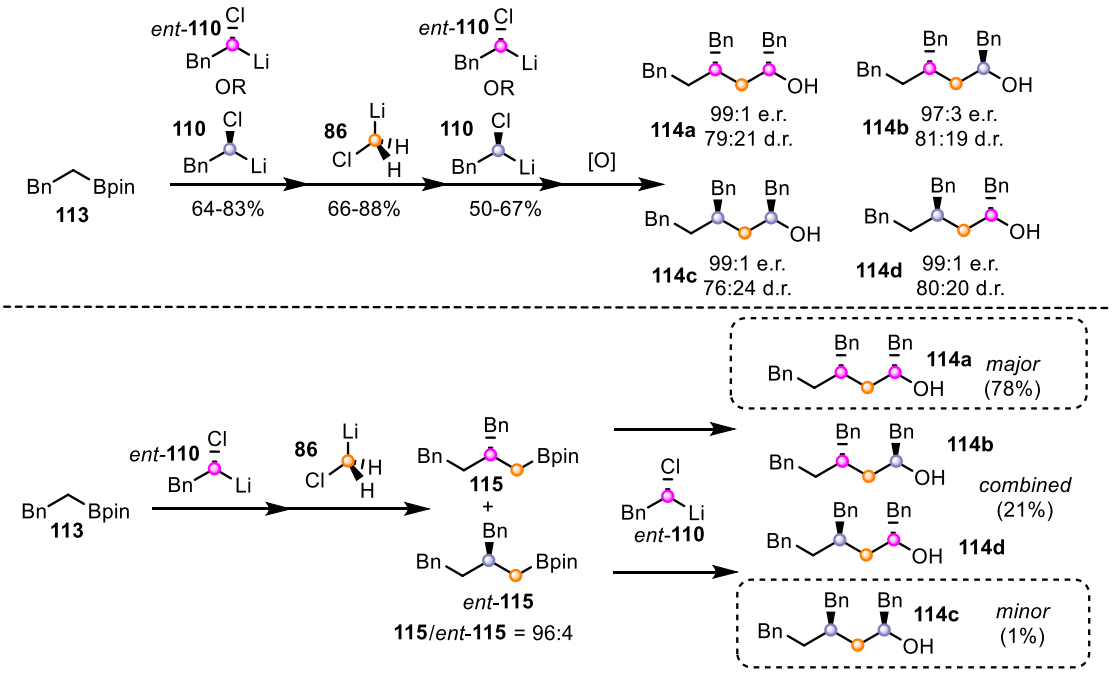
Table 4. Homologation of boronic ester **111** with sulfoxide derived carbenoids



Entry	Organometallic Conditions		Yield (%)	ee (%)
1	EtMgCl	*ex-situ*	49	82
2	^{n}BuLi	*in-situ*	70	96
3	^{n}BuLi	*ex-situ*	0	n.d.

Following this initial result, Blakemore and co-workers reported the iterative reagent-controlled homologation of boronic ester **113**, which enabled the stereoselective synthesis of all four diastereomers of alcohol **114** (Scheme 21).[66] Therein, a four-step sequence was performed, consisting of homologation of **113** with either carbenoid **110** or *ent*-**110**, generated *in-situ* from sulfoxide–lithium exchange of **94** or *ent*-**94** with ^{t}BuLi. This was followed by a Matteson homologation with carbenoid **86**,[67] after which a further iteration with either carbenoid **110** or *ent*-**110,** followed by oxidation, gave alcohols **114a-d**.

Although intervening chromatography was required, all four diastereomers of alcohol **114** were accessed in good yields. The power of the method was demonstrated by the fact that all four products were obtained with almost complete enantiospecificity, which was attributed to a chiral amplification process during the third homologation.[68] Despite the high enantiomeric ratios (e.r.), products **114a-d** were all isolated as diastereomeric mixtures, which represents a significant limitation of this methodology. Although not described in the report, the low diastereospecificity, which is a result of the third homologation, is likely due to a combination of increased steric hindrance of boronic ester **115** relative to **113**, and low chemical stability of α-chloro carbenoids **110** and *ent*-**110** under the reaction conditions. Due to the increased encumbrance at boron, trapping of the carbenoid becomes sufficiently slow such that carbenoid racemisation can now occur by proton-exchange reactions with the carbenoid precursor **94** (these limitations will be discussed further in section 2.2.).

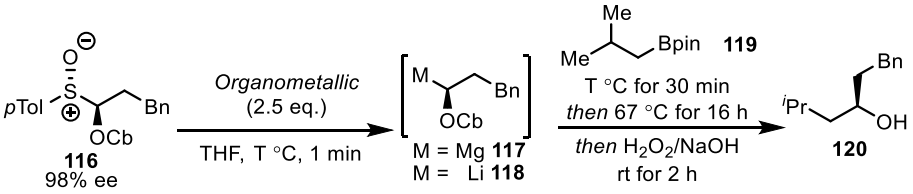


Scheme 21. Iterative homologation sequence and chiral amplification

O'Brien and co-workers have also described the sulfoxide–metal exchange of enantioenriched α-sulfinyl carbamate **116**, which was achieved with either "turbo Grignard" (^{i}PrMgCl•LiCl) or ^{n}BuLi. Carbenoids **117** and **118** were found to react with boronic ester **119** to afford, after oxidation, alcohol **120** with high stereofidelity (Table 5).[69] As part of this study, the authors showed that magnesium carbenoid **117** was configurationally stable at room temperature (rt) for up to 30 minutes, which means that

the reduced stereospecificity in Entry 1 must be due to the reaction of **119** with *rac*-**117**, which is generated upon warming to 67 °C.

Table 5. α-Sulfinyl carbamates as carbenoid precursors for the homologation of boronic esters



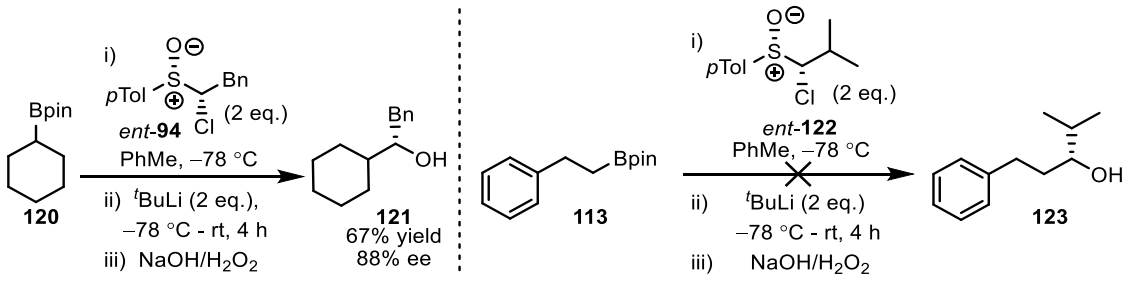
Entry	Organometallic	T (°C)	Yield (%)	ee (%)
1	turbo Grignard	0	68	88
2	^{n}BuLi	–78	72	98

3.2. Project Outline

Molecules that bear contiguous stereocentres are prevalent throughout nature and therefore synthetic methodologies that facilitate access to these structural motifs are of great value. In particular, an iterative process based on the reagent-controlled homologation of boronic esters that employs different building-blocks is attractive, as it would enable the successive introduction of new functional groups with complete control of stereochemistry at each carbon centre.

It has already been demonstrated that α-stannyl benzoates, (*R*)-**69** and (*S*)-**69**, can be used to effect such a process.[70] However, the synthesis of these carbenoid precursors requires stoichiometric amounts of either (+)- or (–)-sparteine (**21**), both of which are expensive and have become difficult to source commercially.[71] Synthetically, the stannanes also fall short of the requirements of such a process, as only the methyl-substituted α-stannyl benzoate has been found to be crystalline. Without the ability to recrystallize, the enantiopurity of the other building-blocks falls below the benchmark (e.r. = 99:1), and hence their utilisation in an iterative homologation process would result in diastereomeric mixtures. Finally, concerns over the toxicity of these organotin reagents, and their by-products, has limited their uptake by the wider synthetic community.

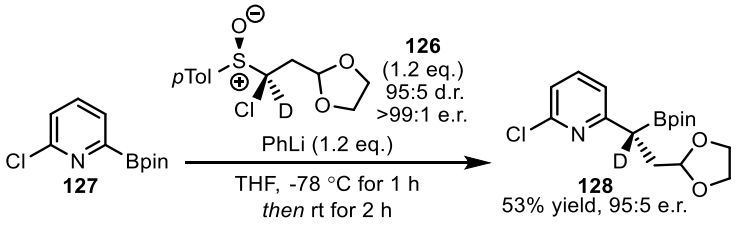
The α-chlorosulfoxides of Blakemore do not share the same toxicity issues and are known to be readily accessible in enantiopure form from commercial materials.[72-74] However, the prospect of α-chlorosulfoxides as carbenoid precursors for an iterative process looks bleak, owing to their poor reactivity profile.[75] Indeed, Blakemore *et al.* have shown that, when the steric hindrance of the α-chlorosulfoxide and/or boronic ester is increased, deprotonation of the parent sulfoxide by the *in-situ* generated carbenoid becomes the dominant reaction pathway, which results in under-homologation (Scheme 22).[66][76]



Scheme 22. Limitations of α-chlorosulfoxide building blocks

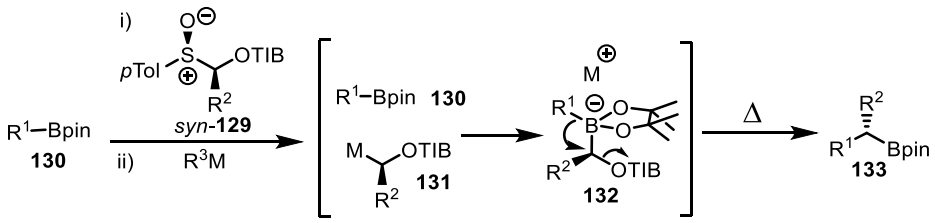
We hoped that α-sulfinyl benzoates might fall upon the middle-ground. The metallated benzoates, which would be generated by sulfoxide–metal exchange, are known to be configurationally stable and have been employed previously for the homologation of boronic esters.[77] Moreover, this type of building-block would allow the aforementioned properties of sulfoxides to be exploited, namely, that they can be prepared with suitable enantiopurity without the need for expensive chiral diamines and, in comparison to stannanes, they are relatively non-toxic.

Initially, this project will be concerned with the preparation of enantioenriched α-sulfinyl benzoates. For a successful iterative homologation process to be realised, these building-blocks must be diastereomerically and enantiomerically pure, otherwise complex product mixtures will result. For example, Blakemore has reported that while α-chlorosulfoxide **126** could be prepared in enantiomerically pure form, it could not be isolated as a single diastereomer (Scheme 23).[78] As a result, the product of the reaction with boronic ester **127** was obtained as a mixture of enantiomers.



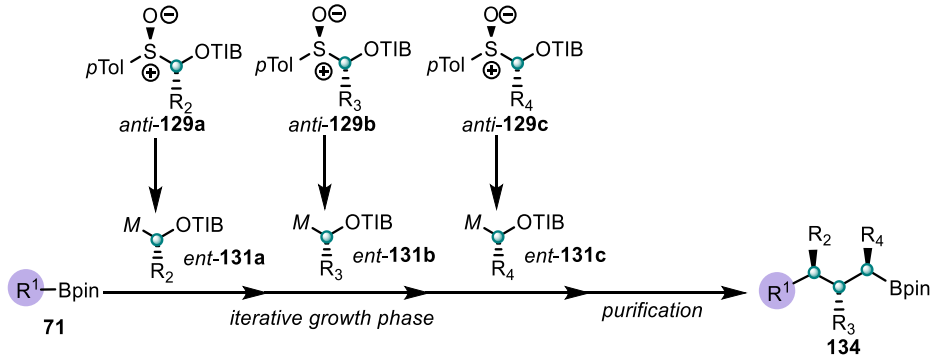
Scheme 23. Diastereomeric impurity in sulfoxide **126** leads to reduced e.r. in boronic ester **128**

The feasibility of using enantioenriched α-sulfinyl benzoates as carbenoid precursors will then be investigated. We anticipate that preparation of the lithiated benzoates by sulfoxide–metal exchange using *in-situ* conditions, that is treatment of α-sulfinyl benzoate *syn*-**129** with a suitable organometallic in the presence of boronic ester **130**, will generate carbenoid species **131** (Scheme 24). This reactive intermediate should be immediately trapped by boronic ester **130** to form boronate complex **132**, which, upon warming, should undergo 1,2-metallate rearrangement to give homologated boronic ester **133**. To re-iterate, we required the rearrangement to only occur in an environment where carbenoid **131** had decomposed in order to avoid over-homologation.



Scheme 24. α-Sulfinyl benzoates as carbenoid precursors for the homologation of boronic esters

The next objective is to validate that a range of α-sulfinyl benzoates, bearing different functional groups, can be employed for the homologation of boronic esters. Finally, we aim to achieve the ambitious goal of an iterative homologation sequence, which employs multiple α-sulfinyl benzoate building-blocks (Scheme 25). We desire a procedure that involves more than one building-block and just a single chromatographic purification at the end of the sequence, which we hope will deliver the desired product in high yield and as a single stereoisomer.



Scheme 25. Iterative homologation sequence using α-sulfinyl benzoates

3.3. Results & Discussion

3.3.1. *Notes on Collaboration*

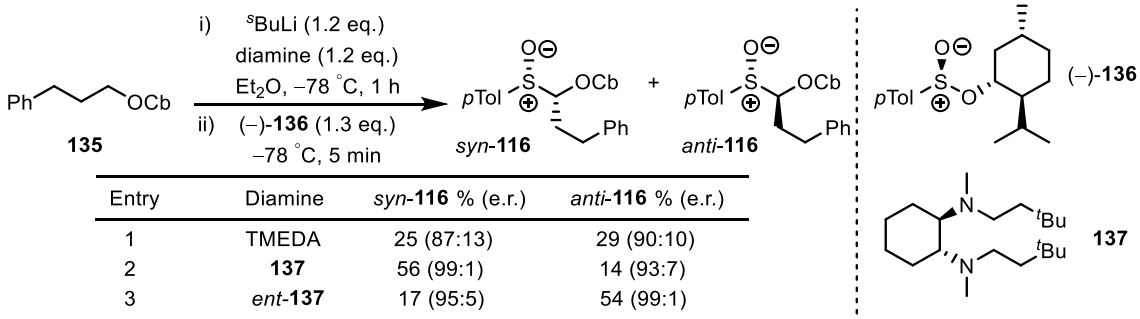
The data presented in this section has been published in part in the following full article: Casoni, G.; Kucukdisli, M.; Fordham, J. M.; Burns, M.; Myers E. L.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2017**, *139*, 11877−11886. Where indicated (*), the data presented was obtained by either Dr. Giorgia Casoni, Dr. Murat Kucukdisli or Dr. Matthew Burns, and is included in this thesis to provide a complete picture of the work.

3.3.2. *Synthesis of Enantioenriched α-Sulfinyl Benzoates*

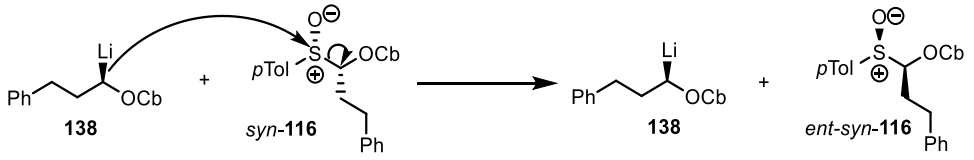
3.3.2.1. Preparation *via* Lithiation–Transmetallation–Trapping

To begin, we considered O'Brien's approach to the synthesis of enantioenriched α-sulfinyl carbamates *syn*- and *anti*-**116**.[69] The authors found that upon lithiation of carbamate **135** with ^{s}BuLi in the presence of TMEDA (**27**), and trapping with (–)-Andersen's sulfinate (**136**) under reverse addition conditions (addition of the lithiated carbamate to a solution of sulfinate **136**), the products *syn*- and *anti*-**116** were obtained with moderate levels of enantioenrichment (Table 6). The presence of the minor enantiomer, *ent*-**116**, was attributed to a sulfinyl-transfer pathway whereby lithiated carbamate **138** reacts with product **116** (Scheme 26). The authors found that, through employment of chiral diamines (*R*,*R*)-*N*,*N'*-bis(3,3-dimethylbutyl)-*N*,*N'*-dimethylcyclohexyldiamine (**137**) and *ent*-**137**, this side-reaction could be overcome to give both *syn*-**116** and *anti*-**116** with high enantiospecificity.

Table 6. O'Brien's synthesis of *syn*- and *anti*-**116**



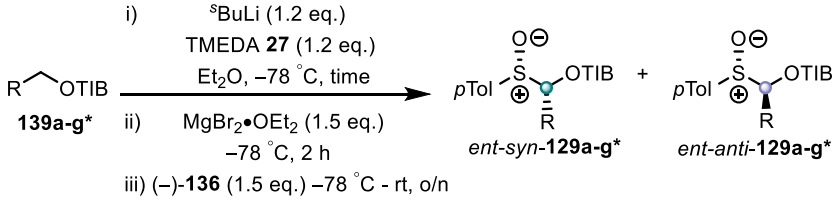
Entry	Diamine	*syn*-**116** % (e.r.)	*anti*-**116** % (e.r.)
1	TMEDA	25 (87:13)	29 (90:10)
2	**137**	56 (99:1)	14 (93:7)
3	*ent*-**137**	17 (95:5)	54 (99:1)

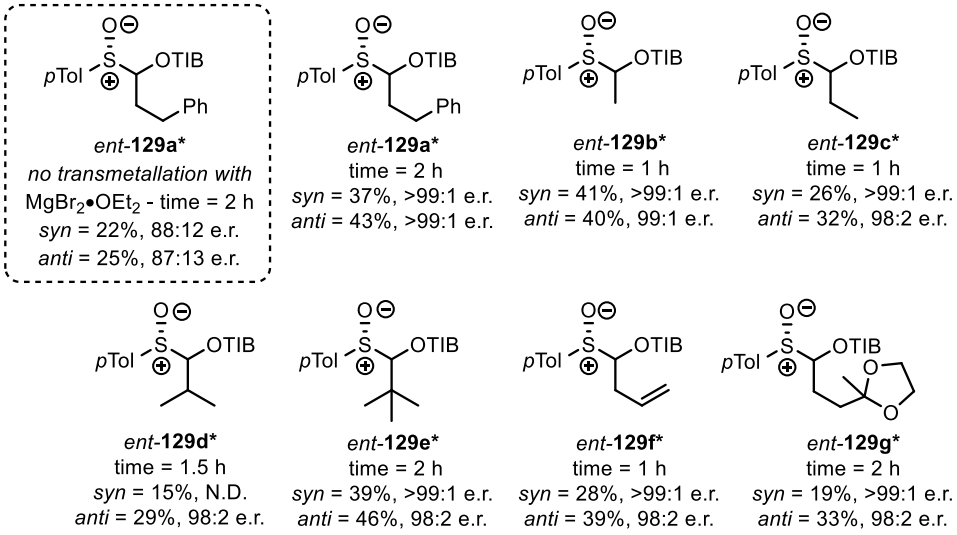


Scheme 26. Double inversion pathway

Indeed, when O'Brien's conditions with TMEDA (**27**) were applied to TIB ester **139***, the desired products *ent-syn*- and *ent-anti*-**129a*** were isolated with unsatisfactory enantiopurity (Table 7). We were reluctant to adopt O'Brien's approach, as it would make us reliant on the use of a chiral diamine. To overcome the sulfinyl-transfer pathway, we wondered whether the less reactive Grignard reagent would have suitably moderated reactivity that would shut down the double-inversion pathway. To our delight, transmetallation of the lithiated benzoate with $MgBr_2$•OEt_2 and subsequent trapping with (–)-**136** gave enantioenriched α-sulfinyl benzoates *ent*-**129a-g***.

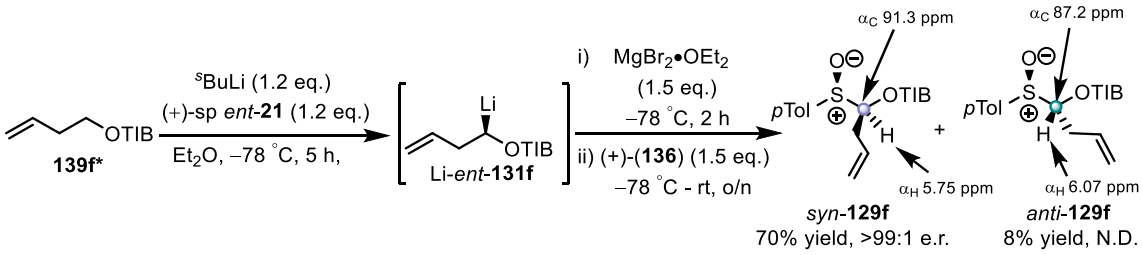
Table 7. Scope for the lithiation–transmetallation–sulfinylation reaction





The relative stereochemistry at the carbon centre of the α-sulfinyl benzoates **139** were assigned based on the results of a modified procedure, which utilised *ent*-(**21**) as the diamine (Scheme 27). Enantioselective lithiation of TIB ester **139f*** gave lithium carbenoid Li-*ent*-**131f** which, after transmetallation and trapping with (+)-Andersen's

sulfinate *ent*-(**136**), gave α-sulfinyl benzoate *ent*-*syn*-**129f** as the major product. Based on this experiment and comparison with the results depicted in Table 7, the following trends were identified. Firstly, there is a correlation between the polarity and the relative configuration of the α-sulfinyl benzoates. More precisely, the *syn*-isomer was always found to be less polar than the *anti*-isomer. Furthermore, the chemical shift of the α-sulfinyl proton (α_H) was always more down-field for the *anti*-isomer, whilst the chemical shift of the α-sulfinyl carbon (α_C) was always more down-field for the *syn*-isomer. These general trends were applicable to all α-sulfinyl benzoates **129** and were used to determine their relative configurations (For a direct comparison of these properties see Table S1).

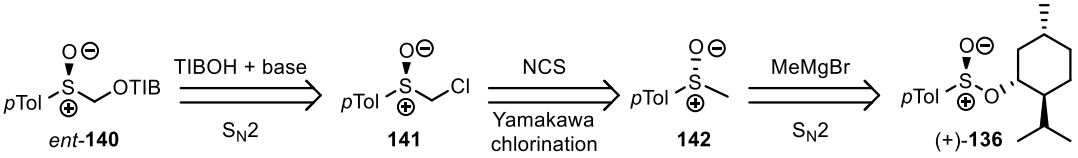


Scheme 27. Determination of configuration by asymmetric lithiation with (+)-sp

We required a range of α-sulfinyl benzoates in order to fully explore the scope of carbenoids that could be employed for the homologation of boronic esters. While the aforementioned method enabled the synthesis of α-sulfinyl benzoates containing aryl (**129a***), alkyl (**129b-e***), alkenyl (**129f***), and ketal (**129g***) functionality, it could not be applied to the synthesis of α-sulfinyl benzoates bearing groups that are sensitive towards lithiation. This was unsatisfactory, because carbenoids that bear sensitive functionality, which have historically performed poorly in lithiation–borylation, were expected to be better tolerated when generated by sulfoxide–metal exchange under *in-situ* conditions. We were therefore keen to develop a method that would provide access to α-sulfinyl benzoates of this type.

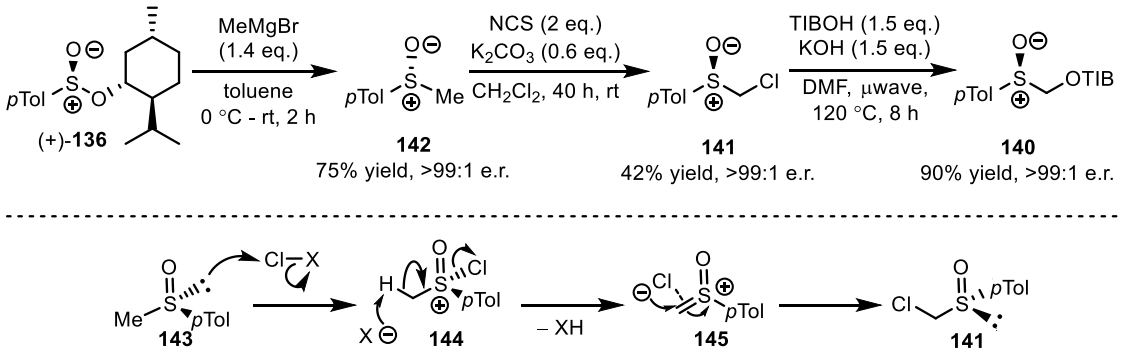
3.3.2.2. Preparation *via* Alkylation

For a new approach towards enantioenriched α-sulfinyl benzoates, we considered the α-alkylation of α-sulfinyl benzoate **140**. Satoh and co-workers had previously demonstrated that the corresponding α-chlorosulfoxide **141** could be deprotonated using mild bases, such as LDA and lithium hexamethyldisilazide (HMDS), conditions which should be more compatible with sensitive functional groups.[79] α-Chlorosulfoxide **141** can be synthesised in two steps from (+)-**136**, *via* Grignard addition and Yamakawa chlorination.[72] We expected that subsequent S_N2 reaction with 1,3,5-triisopropylbenzoic acid (TIBOH) would provide α-sulfinyl benzoate **140** (Scheme 28).



Scheme 28. Retrosynthetic analysis of **140**

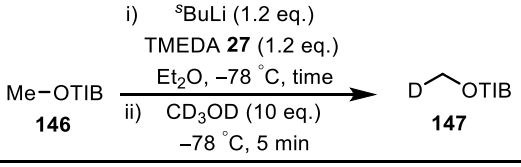
Treatment of (+)-**136** with MeMgBr gave sulfoxide **142** in good yield and enantiospecificity (Scheme 29). Subsequent chlorination using conditions developed by Yamakawa and co-workers, *N*-chlorosuccinimide (NCS) and K_2CO_3, gave α-chlorosulfoxide **141**.[72] This stereoinvertive chlorination reaction suffers from partial racemisation at sulfur and therefore the enantiopurity must be enhanced by recrystallization, which results in a low yield of **141**. Notably, if K_2CO_3 is not employed then the reaction is complete in 2 h and the product is isolated as a racemic mixture. A mechanism for the Yamakawa chlorination reaction was proposed by Blakemore and co-workers.[76] Firstly, sulfoxide **142** is chlorinated by NCS to generate intermediate **143**, which is subsequently deprotonated to give sulfur ylide **144**. A subsequent 1,2-electrophilic rearrangement affords α-chlorosulfoxide **141** *via* contact ion pair **145**. The rehybridization process that occurs upon addition of chloride to thioxocarbenium ion **144** accounts for the inversion of configuration at sulfur. Partial racemisation observed under reaction conditions was attributed to solvent separation of contact ion pair **145** and/or intervention of a radical pathway for the rearrangement. We were pleased to find that when α-chlorosulfoxide **141** was added to a pre-mixed solution of TIBOH and KOH in *N*,*N*-dimethylformamide (DMF), and the reaction mixture was heated under microwave (μwave) irradiation, α-sulfinyl benzoate **140** was obtained in excellent yield and as a single enantiomer.



Scheme 29. Synthesis of α-sulfinyl benzoate **140** and Blakemore's mechanism for the Yamakawa chlorination

Despite now having ready access to our desired intermediate **140**, we were concerned with several aspects of our route. The overall process was time-consuming and low yielding, due to the recrystallisation step that was required following Yamakawa chlorination. We then recognised that α-sulfinyl benzoate **140** should be accessible in a single step from TIB ester **146**, using our lithiation–transmetallation–trapping conditions. Beak and co-workers had previously shown that TIB ester **146** could be lithiated and subsequently trapped with electrophiles.[80] Deuteration studies indicated that lithiation of TIB ester **146** proceeded quickly and that the lithiated species was reasonably stable, which was reflected by good recovery of the deuterated compound **147** (Table 8).

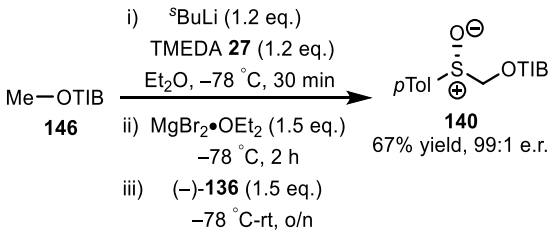
Table 8. Lithiation–Deuteration of TIB ester **146**



Entry	Time (h)	Deuteration (%)	Recovery (%)
1	0.5	100	80
2	1	100	78
3	2	100	75

[a] Deuterium incorporation and percentage recovery determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethyoxybenzene as internal standard.

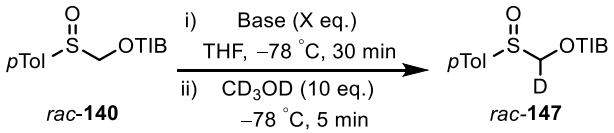
We were delighted to find that subjection of TIB ester **146** to our previously described lithiation–transmetallation–trapping conditions gave α-sulfinyl benzoate *ent*-**140** in good yield (Scheme 30). Traces of starting material were detected in the crude reaction mixture, as were small amounts of TIBOH, which was indicative of a minor α-elimination pathway.[81]



Scheme 30. Synthesis of α-sulfinyl benzoate **140** by lithiation–transmetallation–trapping

With α-sulfinyl benzoate **140** in hand we began alkylation studies. As a starting point, we investigated the deprotonation of α-sulfinyl benzoate *rac*-**140** (for preparation details see section 6.3.) with LiHMDS, LDA, and Knochel-Hauser base (TMPMgCl•LiCl)[82] (Table 9). Interestingly, complete deuterium incorporation was only achieved upon use of 2.00 equivalents of base (Entry 3). Furthermore, the lithiated species was found to be relatively unstable, reflected by a surprisingly low recovery of α-sulfinyl benzoates *rac*-**140** and *rac*-**147** after aqueous work-up, when compared to the corresponding magnesiated species.

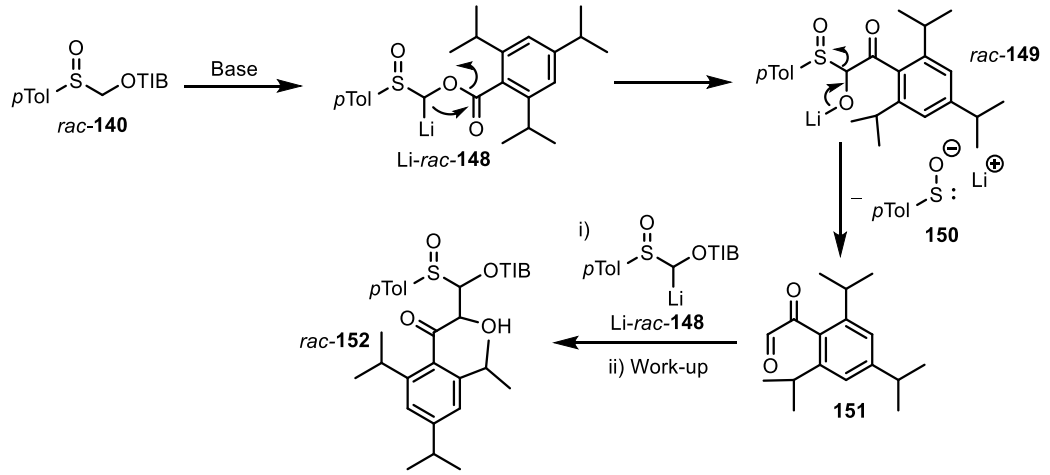
Table 9. Deprotonation studies of α-sulfinyl benzoate *rac*-**140**



Entry	Base (eq.)	Deuteration (%)	Recovery (**140** + **147**)(%)
1	LDA (1.05)	36	88
2	LiHMDS (1.05)	46	90
3	LiHMDS (2.00)	100	90
4	TMPMgCl•LiCl (1.05)	66	98
5	TMPMgCl•LiCl (2.00)	90	96

Deuterium incorporation and percentage recovery (*rac*-130 + *rac*-133) determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethyoxybenzene as internal standard.

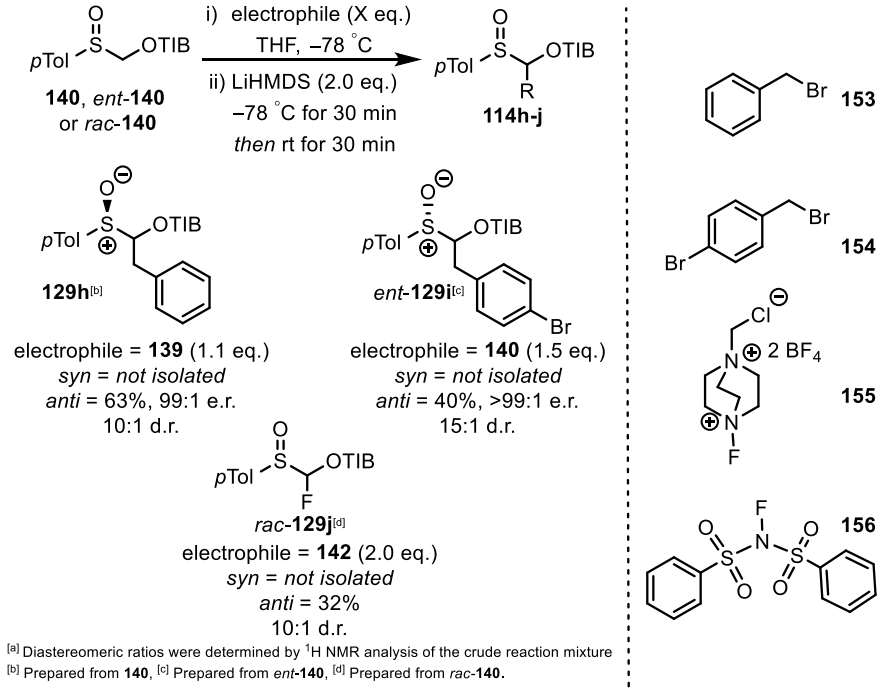
Having observed side-product *rac*-**152** by ^{1}H nuclear magnetic resonance (NMR) analysis of the crude mixture, we propose that decomposition occurs *via* 1,2-Wittig rearrangement of lithiated α-sulfinyl benzoate Li-*rac*-**148**, a process that has been previously observed for lithiated carbamates (Scheme 31).[83] Following rearrangement, elimination of sulfenate **150** would give α-ketoaldeyde **151**, which might react with a second equivalent of Li-*rac*-**148** to give side-product *rac*-**152**. It seems that the corresponding magnesiated species is more stable towards this type of rearrangement (Table 9, Entries 4-5).

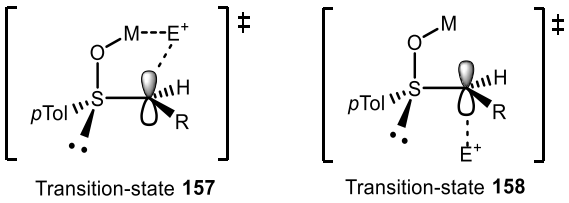


Scheme 31. Decomposition pathway of lithiated α-sulfinyl benzoate Li-*rac*-**148**

Having identified conditions for the deprotonation–deuteration of α-sulfinyl benzoate **140**, we began to explore the scope of electrophiles. Pleasingly, using the optimum deuteration conditions (Table 9, Entry 3), benzyl bromides **153** and **154** were found to give α-sulfinyl benzoates *anti*-**129h** and *ent-anti*-**129i** in good yields (Table 10). This method also facilitated the synthesis of *rac-anti*-**129j**, however reaction success was highly dependent on the source of electrophilic fluorine. When Selectfluor (**155**) was employed, only starting material and side-product *rac*-**140** were observed, which was attributed to poor solubility of **155**. However, switching to *N*-fluorobenzenesulfonimide (NFSI) (**156**), which is partially soluble in THF, gave *rac-anti*-**129j** in synthetically useful quantities. The high diastereoselectivity of the alkylation and fluorination reactions precluded isolation of *syn*-products **129h-j**. The stereoselective reactions of α-sulfinyl carbanions are well documented and have previously been accounted for on the basis of two transition-states (Scheme 32).[84-85] If the electrophile is able to coordinate to the counter-cation of the deprotonated species **157**, which is known to reside on the oxygen of the sulfoxide,[86] the electrophile approaches along the top face and the *syn*-product is obtained. Alternatively, if the product is unable to coordinate to the counter-cation, then approach occurs from the less sterically hindered face to give the *anti*-product. Although this model accounts for the observed stereoselectivity for **129h** and **129i**, it would be expected that NFSI (**156**) would coordinate to the counter-cation as in transition-state **158**, and thus lead to *syn*-**129j** predominantly. However, this was not the case and it is therefore likely that other factors are dictating the stereochemical outcome. For instance, it is possible that the adjacent benzoate group influences the conformation of the lithiated species in solution, and therefore affects the approach of incoming electrophiles.

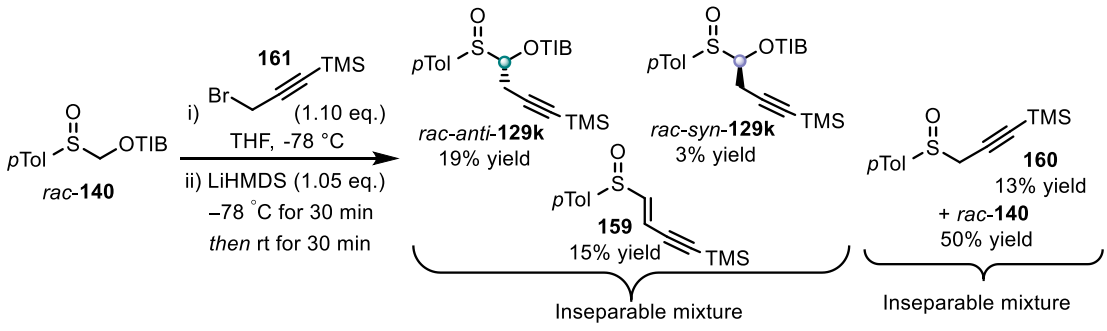
Table 10. Synthesis of α-sulfinyl benzoates **129h-j**





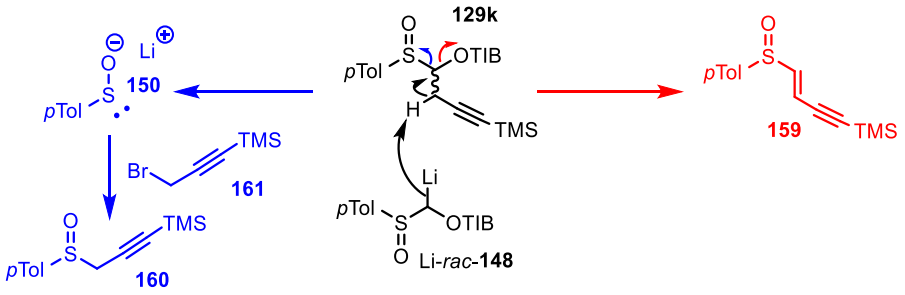
Scheme 32. Predicting stereoselectivity in the reactions of α-sulfinyl carbanions

We were also interested in the synthesis of propargylic α-sulfinyl benzoate **129k**, however LiHMDS was found to be an unsuitable base to effect this transformation (Scheme 33). While products *rac-syn-* and *rac-anti-***129k** could be observed, they were obtained as an inseparable mixture with side-product **159**. The major species was identified as *rac*-**140**, which was recovered as a mixture with sulfoxide side product **160**.



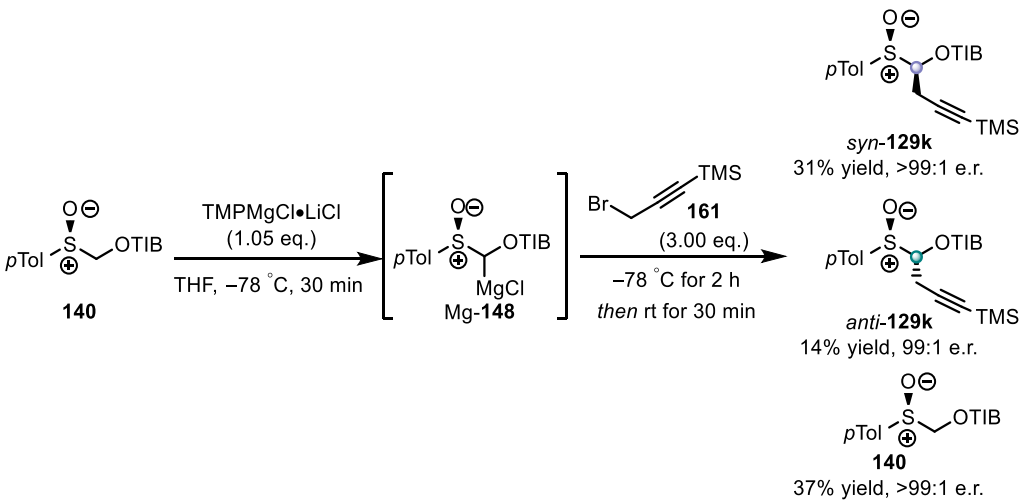
Scheme 33. Attempted synthesis of *rac-syn-***129k** and *rac-anti-***129k**

The proposed origin of impurities **159** and **160** has been outlined in Scheme 34. It is likely that both side-products arise from an E2 reaction of product *rac*-**129k**. We rationalised that if LiHMDS was behaving as the base in this competing pathway, then performing the reaction under *ex-situ* conditions, that is addition of LiHMDS to *rac*-**140** followed by addition of **161**, should overcome the side reaction. However, with this modified procedure the same result was obtained, which suggested that Li-*rac*-**148** was reacting with product **129k**.



Scheme 34. Origin of side-products **159** and **160**

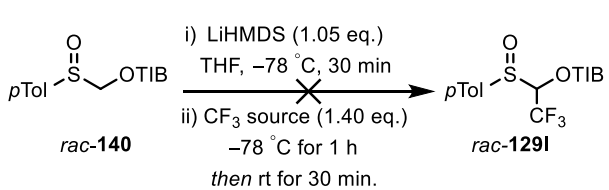
We turned to the Knochel-Hauser base with the reasoning that a less reactive magnesiated species Mg-*rac*-**148**, obtained upon deprotonation, might be less likely to participate in this product-eroding reaction. We were wary that the Knochel-Hauser base might react with **129k** directly, and therefore elected to perform the reaction under *ex-situ* conditions (Scheme 35). The reaction was carried out with 1.05 equivalents of base, which led to synthetically useful quantities of *syn*-**129k** and *anti*-**129k**. Starting material *ent*-**140** was also recovered in enantiopure form. Further attempts to improve yield by employing additional base resulted in a messy reaction that precluded the isolation of product. Curiously, Mg-*rac*-**148** gave the opposite diastereoselectivity to the corresponding lithiated species, as the *syn*-product was now formed preferentially.



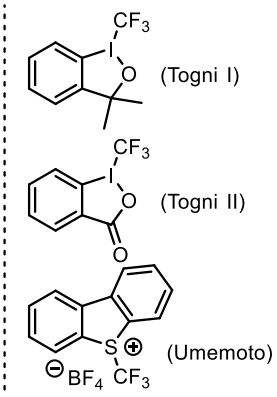
Scheme 35. Synthesis of α-sulfinyl benzoates *ent-syn*-**129k** and *ent-anti*-**129k**

Next, we turned our attention to the preparation of α-sulfinyl benzoate *rac*-**129l** (Table 11). Togni had previously reported the electrophilic trifluoromethylation of enolates.[87] We wondered whether an α-sulfinyl carbanion Li-**148**, generated by deprotonation of *rac*-**140** with LiHMDS, might react in a similar manner. Unfortunately, trifluoromethylation was not achieved with this method for a range of trifluoromethyl sources (Entries 1-3) and starting material *rac*-**140** was identified as the major component of the crude reaction mixture in all cases.

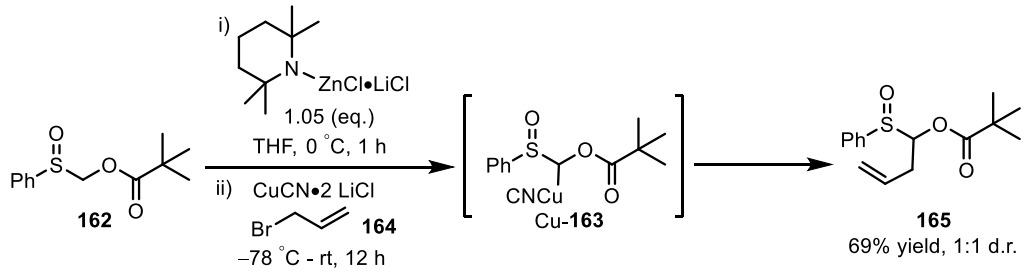
Table 11. Attempted synthesis of *rac*-**129l** *via* trifluoromethylation of Li-**148**



Entry	CF_3 source	Comments
1	Togni I	SM major peak, messy crude
2	Togni II	SM major peak, messy crude
3	Umemoto	SM major peak, messy crude



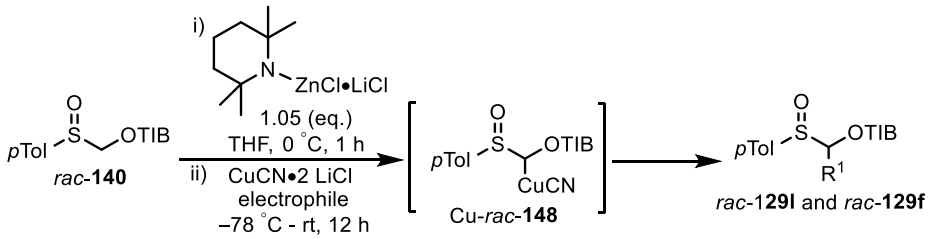
The mechanism by which these electrophilic trifluoromethylating agents react has long been debated and it is still not fully understood whether their reactions occur *via* radical or polar pathways.[88-89] With this in mind we turned our attention to the efforts of Knochel and co-workers (Scheme 36).[90] They had previously reported that a similar sulfoxide **162** could be transformed into cuprate Cu-**163** and alkylated with allyl bromide **164**.



Scheme 36. Knochel's synthesis of **165** *via* cuprate Cu-**163**

We reasoned that if a radical process was required for trifluoromethylation, reaction success might be realised with a cuprate intermediate.[91-92] In order to investigate this, two reactions were performed in parallel (Table 12). The first involved attempted trapping of cuprate Cu-*rac*-**148** with the Togni II reagent, the second involved alkylation with allyl bromide as a means of investigating whether Cu-*rac*-**148** had formed. Unfortunately, the reaction with Togni II did not provide access to α-sulfinyl benzoate **129l** and, after quenching of the reaction and an aqueous work-up, full recovery of starting material *rac*-**140** was achieved. On the other hand, trapping with allyl bromide gave *rac*-**129f** with good conversion. Considering these results, we decided to turn our attention towards the synthesis of other substrates.

Table 12. Attempted synthesis of *rac*-**129l** *via* trifluoromethylation of Cu-*rac*-**148**

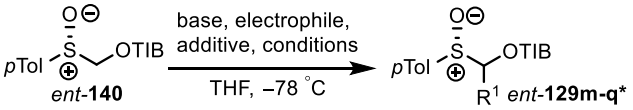


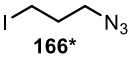
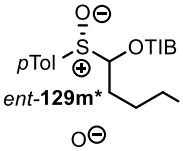
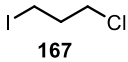
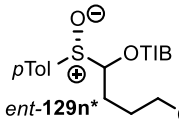
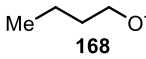
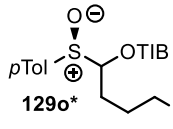
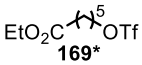
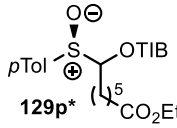
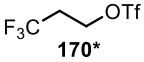
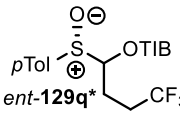
Entry	Electrophile	R^1	P:SM[a]	*syn*:*anti*
1	Togni II	$-CF_3$ (*rac*-**129l**)	0:100	N/A
2	allyl bromide **164**	$-CH_2CH{=}CH_2$ (*rac*-**114f**)	52:48	1:1

[a] Conversion to product measured by ^{1}H NMR analysis of the crude reaction mixture
[b] Diastereomeric ratio measured by ^{1}H NMR analysis of the crude reaction mixture

Unfortunately, it was difficult to find general conditions to alkylate α-sulfinyl benzoate **140** however, after some screening, α-sulfinyl benzoates *ent*-**129m-q*** were prepared (Table 13). Having achieved our target of preparing carbenoid precursors bearing functional groups sensitive towards lithiation, we sought to utilise the building blocks for the homologation of boronic esters.

Table 13. Synthesis of α-sulfinyl benzoates **129m-q***



Entry	Electrophile (eq.)	Base (eq.)	Additive (eq.)	Conditions	114*
1	 **166*** (2.00)	LDA (2.00)	HMPA (2.00)	*in-situ*	 *syn* = 11%, 99:1 e.r. *anti* = 25%, >99:1 e.r.
2	 **167** (2.00)	LDA (2.00)	HMPA (2.00)	*in-situ*	 *syn* = *not isolated* *anti* = 40%, 99:1 e.r.
3	 **168** (1.10)	NaHMDS (1.05)	none	*in-situ*	 *syn* = 42%, 98:2 e.r. *anti* = 36%, 98:2 e.r.
4	 **169*** (1.30)	NaHMDS (1.50)	none	*in-situ*	 *syn* = 29%, 99:1 e.r. *anti* = 27%, 99:1 e.r.
5	 **170*** (3.00)	TMPMgCl•LiCl (1.10)	none	ex-*situ*	 *syn* = 28%, >99:1 *anti* = *not isolated*

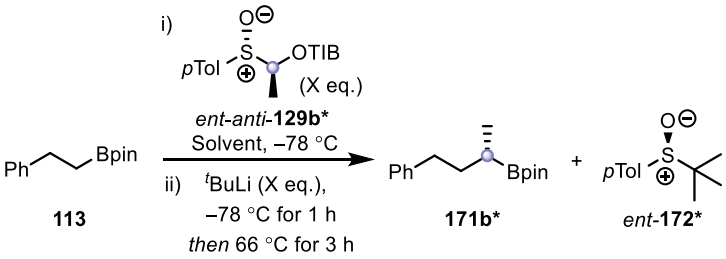
* α-Sulfinyl benzoates **114m-q*** were prepared by Dr. Giorgia Casoni and Dr. Murat Kucukdisli.

3.3.3. *Homologation of Boronic Esters with Carbenoids Derived from Enantioenriched α-Sulfinyl Benzoates*

3.3.3.1. Reaction Optimisation

The homologation conditions were optimised by Dr. Giorgia Casoni and the results are summarised in Tables 14 and 15.

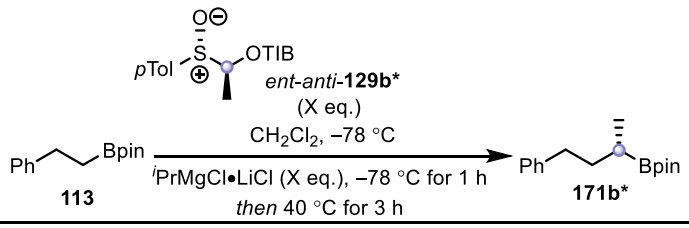
Table 14. Optimisation of homologation conditions for a lithium carbenoid (^{t}Butyl methyl ether (TBME))



Entry	^{t}BuLi (eq.)	*ent-anti*-**129b*** (eq.)	Solvent	Conversion[a] **171b***:**113**
1	1.4	1.50	THF	92:8
2	1.4	1.50	Et_2O	20:80
3	1.4	1.50	TBME	58:42
4	1.4	1.50	PhMe	55:45
5	2.0	1.50	THF	96:4
6	2.0	1.20	THF	97:3
7	2.0	1.05	THF	99:1 (73)[b]

[a] Conversion determined by GCMS analysis of the crude reaction mixture
[b] Number in parentheses represent isolated yield after column chromatography

Table 15. Optimisation of homologation conditions for a magnesium carbenoid

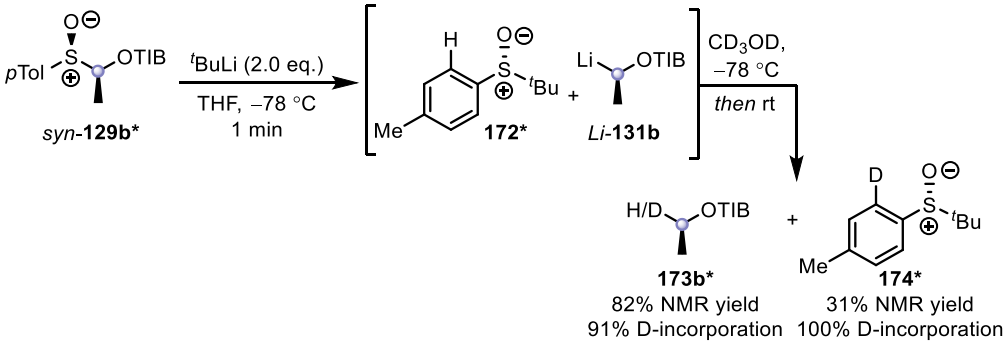


Entry	*ent-anti*-**129b*** (eq.)	^{i}PrMgCl•LiCl (X eq.)	Conditions	Conv. **171b***:**113**[a]	Yield (%)
1	1.1	1.2	*ex-situ*	99:1	73[b]
2	1.3	1.2	*ex-situ*	99:1	74[b]
3[c]	1.3	1.2	*in-situ*	99:1	76[d]

[a] Conversion determined by GCMS analysis of the crude reaction mixture
[b] Values represent yield by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard
[c] Reaction performed using *anti*-**129b*** which gave *ent*-**171b***
[d] Value represents isolated yield after column chromatography

* Reaction optimisation was performed by Dr. Giorgia Casoni.

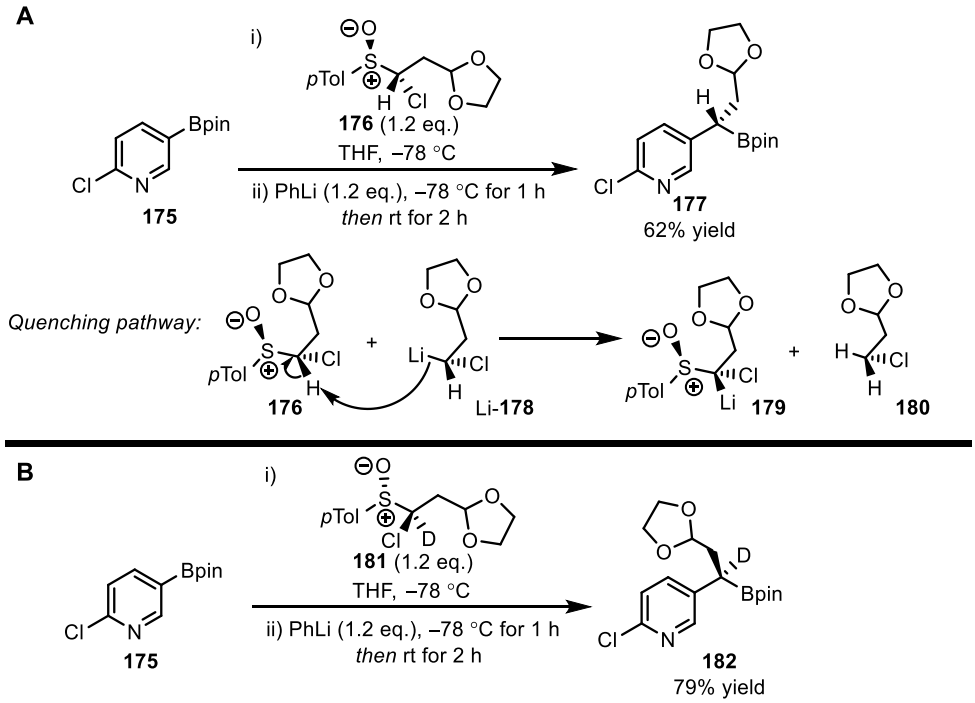
Notably, an excess of ^{t}BuLi is required for optimum reaction success. It was found, in the absence of boronic ester, that the tolyl group of by-product **172*** is lithiated in the position *ortho* to the sulfoxide substituent (Scheme 37). This deprotonation was likely performed by both ^{t}BuLi and the *in-situ* generated carbenoid Li-**131b**. Therefore, under the optimised conditions, excess ^{t}BuLi helps prevent detrimental quenching of the carbenoid by serving as a sacrificial base, as well as ensuring complete sulfoxide–metal exchange.



Scheme 37. Investigation of carbenoid quenching pathways

Curiously, presence of α-sulfinyl benzoate *ent-anti*-**129b*** in a large excess resulted in a less efficient reaction (Table 14, Entries 5 and 6). Blakemore and co-workers previously found that, for their homologation process, the acidic α-proton of α-chlorosulfoxide **176** was able to quench the *in-situ* generated carbenoid Li-**178** (Scheme 38A).[78][93] They overcame this quenching pathway by making use of a primary kinetic isotope effect,[94] whereby use of the corresponding α-deuterated sulfoxide **181** gave improved results for the homologation of boronic ester **175** (Scheme 38B). Whilst the α-proton of the α-sulfinyl benzoates should be less acidic than that of the α-chlorosulfoxides, it might still quench carbenoid Li-*ent*-**131b**. Therefore, it seems that a slight excess of α-sulfinyl benzoate *ent-anti*-**129b*** (1.05 eq.) and a large excess of ^{t}BuLi (2.00 eq.) provides the optimum balance between reaction success and subdual of quenching pathways (Schemes 37 and 38).

* Quenching study performed by Dr. Murat Kucukdisli



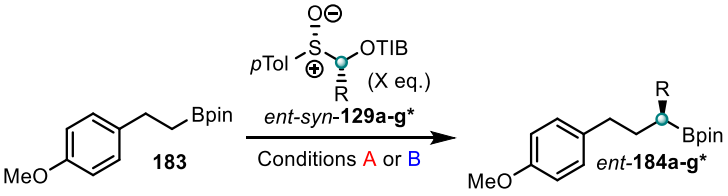
Scheme 38. Blakemore's approach to overcome the α-proton quenching pathway

3.3.3.2. Substrate Scope

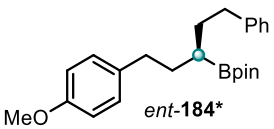
Having optimised the homologation conditions, we began to investigate the scope of the reaction with respect to α-sulfinyl benzoates (Table 16). Substrates *ent-syn*-**129a-c*** gave the corresponding homologation products *ent*-**184a-c*** in good yields with both lithium-carbenoid and magnesium-carbenoid conditions, A and B, respectively. After oxidation to the corresponding alcohols *ent*-[O]-**184a-c***, chiral high-performance liquid chromatography (HPLC) analysis revealed that the products had been generated with complete retention of stereochemical information. The same levels of enantiospecificity were observed when using α-sulfinyl benzoates *ent-syn*-**129f-g*** and the products were obtained in high yields, despite the presence of functionality that might have hindered reaction progress. For α-sulfinyl benzoates *ent-syn*-**129a-c***, **f-g***, lithium-carbenoid conditions were found to be slightly higher yielding than those using the magnesium carbenoid, which was attributed to the higher reactivity of organolithium reagents compared to their organomagnesium counterparts. Increasing the steric hindrance around the carbenoid centre, as for substrates *ent-syn*-**129d-e***, greatly reduced reaction success for both methods A and B. Whilst conditions A did allow for homologation with carbenoid precursor *ent-syn*-**129d***, the yield for this reaction was found to be

significantly lower than for α-sulfinyl benzoates *ent-syn*-**129a-c***, **f-g***. It is likely that now the steric demand of the lithiated species leads to competing quenching processes rather than desired reaction with boronic ester **183**. Furthermore, the enantiospecificity was found to be 97%, slightly lower than what had previously been observed. Due to the increased steric encumbrance, the carbenoid is evidently more long-lived such that racemisation pathways become operative. Unsurprisingly, for this already hindered substrate, conditions B were found to be essentially non-productive and significant amounts of starting boronic ester **183** were observed. Further increasing steric hindrance (*ent-syn*-**129e***) resulted in complete shutdown of desired reactivity and starting material **183** was found to be a major component of the reaction mixture for both sets of conditions. TIB ester **139e*** was also observed as a major component of the reaction mixture meaning that, for very hindered systems, carbenoid quenching is favoured over boronate complex formation.

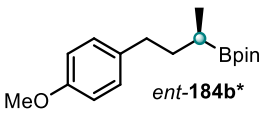
Table 16. α-Sulfinyl benzoates *ent-syn*-**129a-g*** for the homologation of boronic ester **183**



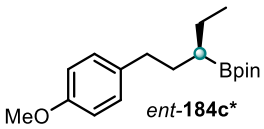
A = ^{t}BuLi (2.00 eq.), **129** (1.05-1.10 eq.), boronic ester (0.2 mmol, 1.00 eq.)
THF, *in-situ*, –78 °C,1 h, *then* 66 °C, 3 h.
B = ^{i}PrMgCl•LiCl (1.20 eq.), **129** (1.30 eq.), boronic ester (0.2 mmol, 1.00 eq.)
CH_2Cl_2, *in-situ*, –78 °C,1 h, *then* 40 °C, 3 h.



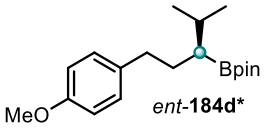
A: 81%, 98:2 e.r., 98% e.s.
B: 71%, >99:1 e.r., 100% e.s.



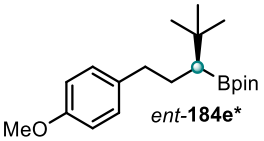
A: 78%, 99:1 e.r., 99% e.s.
B: 58%, >99:1 e.r., 100% e.s.



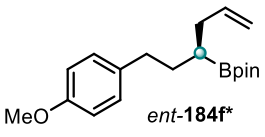
A: 61%, >99:1 e.r., 100% e.s.
B: 49%, >99:1 e.r., 100% e.s.



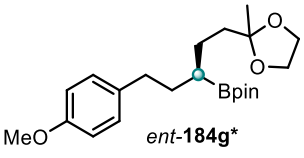
A: 54%, 95:5 e.r., 97% e.s.
B: 8%, 98:2 e.r., 100% e.s.



A: 0%
B: 0%



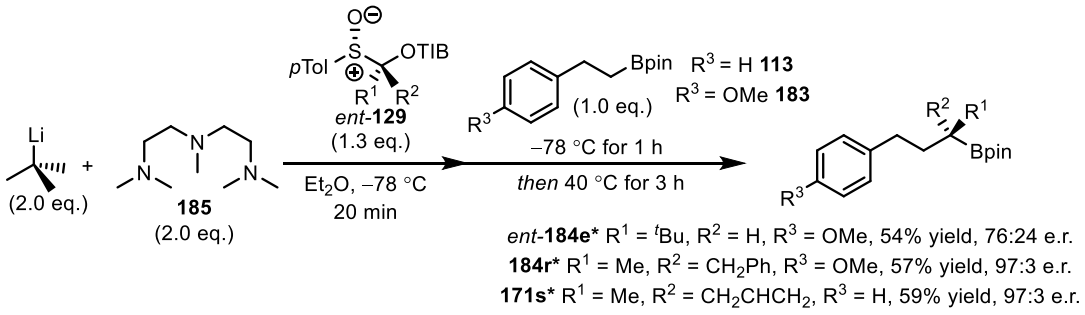
A: 85%, 99:1 e.r., 99% e.s.
B: 69%, >99:1 e.r., 100% e.s.



A: 70%, 99:1 e.r., 99% e.s.
B: 63%, >99:1 e.r., 100% e.s.

* Reactions were performed by Dr. Giorgia Casoni.

This carbenoid quenching process was overcome in part by performing the reaction under "reverse addition" conditions (Scheme 39). A dilute solution of α-sulfinyl benzoate *ent-syn*-**129e*** in Et_2O (0.1 M w.r.t boronic ester) was added slowly to a solution of ^{t}BuLi and triamine **185** in Et_2O at –78 °C and, after twenty minutes, boronic ester **183** was added to give homologation product *ent*-**184e*** in a pleasing yield of 54%, but with an enantiomeric ratio of just 76:24. The low stereofidelity of this reaction was attributed to a proton-transfer process between *ent*-Li-**131e** and *ent-syn*-**129e***, as 3° α-sulfinyl benzoates *ent-anti*-**129r*** and *ent-anti*-**129s*** gave the corresponding products **184r*** and **171s*** in high enantiopurity using this method.



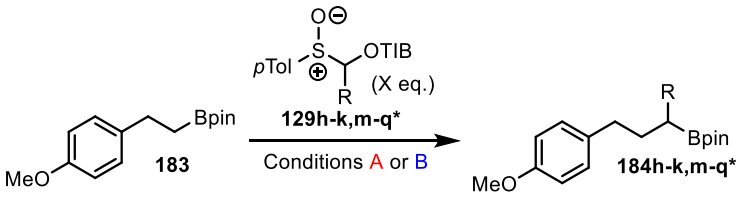
Scheme 39. Reverse addition procedure for the synthesis of *ent*-**184e***, **184r*** and **171s***

We then applied our optimised conditions to enantioenriched α-sulfinyl benzoates **129h-i,k,m-q*** and *rac*-**129j** (Table 17). In general, the milder conditions B were found to be the most useful for these substrates. Where chromatographic separation of boronic ester product **184** and starting material **183** was not possible, the product mixture was oxidised to give the corresponding alcohols in order to facilitate purification. α-Sulfinyl benzoate *anti*-**129h** gave good reaction success with both sets of conditions. Lithium carbenoid conditions were found to be less compatible for *ent-anti*-**129i**, as the reaction resulted in starting boronic ester **183** and proto-debrominated product **184h**, which was detected by GCMS analysis of the reaction mixture. The origin of the reduced stereospecificity under conditions A is puzzling. We suspect that upon lithium-bromine exchange, the intermediate aryllithium can participate in proton-transfer process with α-sulfinyl benzoate *ent-anti*-**129i**, which is subsequently re-protonated to give *ent-syn*-**129i**. After the poor performance of this substrate under conditions A, we were delighted to find that conditions B delivered homologation product **184i** in high yield and with complete

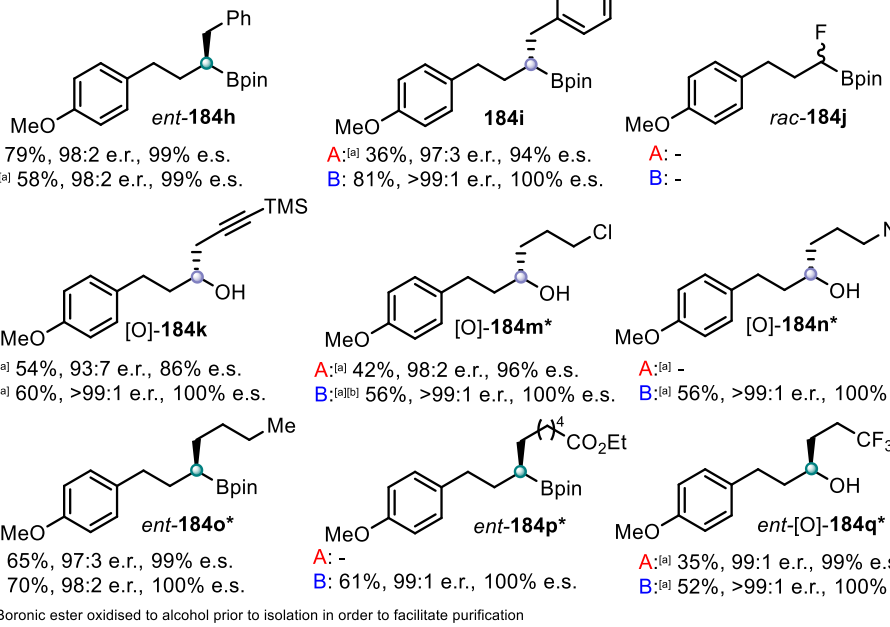
*Reactions performed by Dr. Murat Kucukdisli.

transfer of stereochemical information. Evidently, sulfoxide–magnesium exchange is much faster than magnesium–bromine exchange for this compound, as proto-debrominated product **184h** was not observed. Unfortunately, fluorinated α-sulfinyl benzoate *rac-anti*-**129j** did not provide a route into boronic ester *rac*-**184j** with conditions A or B. The major components of the reaction were identified as proto-desulfinylated material and starting boronic ester **183**. It is likely that the intermediate carbenoid species is sufficiently stabilised, so that trapping with boronic ester **183** is reversible and therefore the metallated species reacts preferentially *via* quenching processes or decomposes *via* α-elimination. It was also found that chloro **129m***, azidyl **129n***, butyl **129o***, ester **129p*** and trifluoromethyl **129q*** containing α-sulfinyl benzoates could be employed in the reaction and, for these substrates, the best results were obtained using conditions B.

Table 17. α-Sulfinyl benzoates **129h-k,m-q*** for the homologation of boronic ester **183**



A = ^{t}BuLi (2.00 eq.), α-sulfinyl benzoate (1.05-1.10 eq.), boronic ester (0.2 mmol, 1.00 eq.), THF, *in-situ*, –78 °C,1 h, *then* 66 °C, 3 h.
B = ^{i}PrMgCl•LiCl (1.20 eq.), α-sulfinyl benzoate (1.30 eq.), boronic ester (0.2 mmol, 1.00 eq.), CH_2Cl_2, *in-situ*, –78 °C,1 h, *then* 40 °C, 3 h.



[a] Boronic ester oxidised to alcohol prior to isolation in order to facilitate purification
[b] *Ex-situ* conditions employed

We were greatly encouraged by the results of this study. It was particularly pleasing to

*Reactions involving **129m-q*** were performed by Dr. Giorgia Casoni and Dr. Murat Kucukdisli.

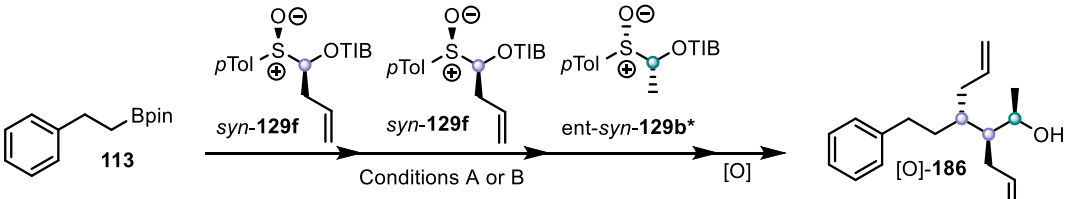
find that, by using both lithium and magnesium carbenoids, a wide range of functional groups could be incorporated into the homologated products with high stereofidelity. Eager to push the boundaries of this methodology, we looked to develop an iterative process that would utilise these α-sulfinyl benzoate building-blocks.

3.3.3.3. *Iterative Homologation Sequence*

To demonstrate the synthetic utility of our homologation protocol, we wanted to perform an iterative homologation sequence that employed different α-sulfinyl benzoate building blocks. Importantly, the homologation reactions must meet the criteria stated at the outset. That is, each iteration must proceed with high efficiency and stereocontrol in order to avoid complex mixtures and thus the need for intervening column chromatography between homologations.

We began by considering a three-step sequence that would employ *syn*-**129f** and *ent-syn*-**129b*** for the homologation of boronic ester **113** with both conditions A and B (Table 18). Importantly, a filtration procedure was to be performed after each homologation reaction in order to remove the sulfoxide–metal exchange by-product, which would otherwise lead to issues in subsequent homologations. In accordance with what had been previously observed, GCMS analysis indicated that the first homologation proceeded smoothly for both sets of conditions. However, due to the increased steric hindrance of the new-formed boronic ester, the second homologation was met with lower levels of efficiency. Whilst the lithium carbenoid still reacted effectively, the conversion for the corresponding magnesiated species was markedly reduced. This reiterates our previous observation that, when the steric hindrance of the system is increased, internal quenching becomes the favoured pathway for magnesium carbenoids. At this stage, we decided to terminate the sequence with conditions B. Upon performing the third iteration with conditions A, we were met with significant amounts of starting boronic ester **113**. Evidently, the hindrance of the boronic ester has reached a point where the efficiency of reaction with a lithium carbenoid deteriorates. As with conditions B, low conversion was attributed to carbenoid quenching, as significant amounts of TIB ester **139b** was observed by ^{1}H NMR and GCMS analysis. This meant that full boronate complex formation was not achieved, which was also confirmed by ^{11}B NMR (Figure 1), and, following oxidation of the crude mixture and column chromatography, product [O]-**186** was isolated in a rather disappointing yield of 29% (65% yield per iteration).

Table 18. Iterative homologation sequence



A = ^{t}BuLi (2.00 eq.), **129** (1.10 eq.), boronic ester (1.00 mmol, 1.00 eq.), THF, *in-situ*, –78 °C,1 h, *then* 66 °C, 3 h.

B = ^{i}PrMgCl•LiCl (1.20 eq.), **129** (1.30 eq.), boronic ester (1.00 mmol, 1.00 eq.), CH_2Cl_2, *in-situ*, –78 °C, 1 h, *then* 40 °C, 3 h.

Entry	Conditions	1st P:SM	2nd P:SM	3rd P:SM[c]	Yield (%)[d]	d.r.[e]
1	A[a][b]	98:2	96:4	60:40	29	>95:5
2	B[a]	99:1	26:74	-	-	-

[a] Conversion to product determined by GCMS analysis of the reaction mixture
[b] The oxidation step was performed using $NaBO_3$•4 H_2O
[c] Performed on 0.33 mmol scale
[d] Yield reported is that of isolated compound following by column chromatography (over the 4 steps)
[e] Diastereomeric ratio was determined by ^{13}C NMR analysis of isolated material

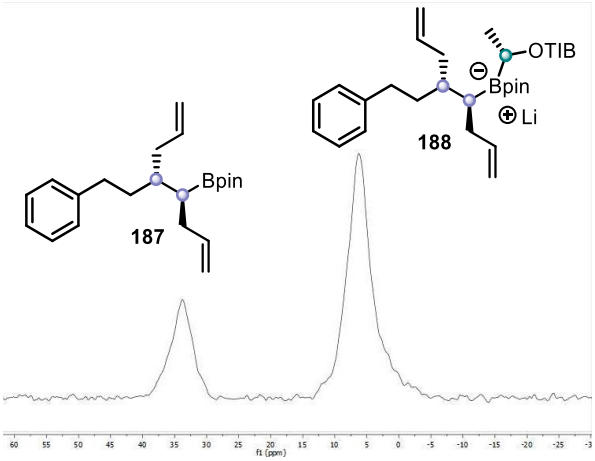
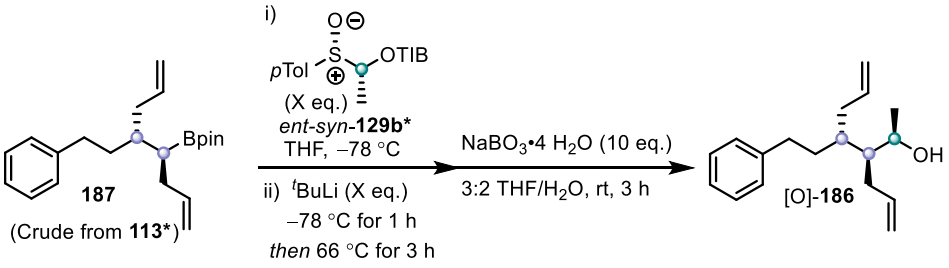


Figure 1. ^{11}B NMR spectrum for the third homologation taken after 1 hour at –78 °C

We were keen to improve upon our initial result for the third homologation. We rationalised that increasing the equivalents of carbenoid should enhance reaction conversion (Table 19). We found that additional amounts of both α-sulfinyl benzoate *ent-syn*-**129b*** and ^{t}BuLi were required to improve reaction success, which enabled product [O]-**186** to be isolated in 41% overall yield (80% yield per iteration), and as a single stereoisomer. Whilst we were delighted with this improvement, GCMS analysis indicated that full consumption of starting material had not been achieved. Despite efforts to push the reaction further towards completion (Entry 4), the yield could not be increased.

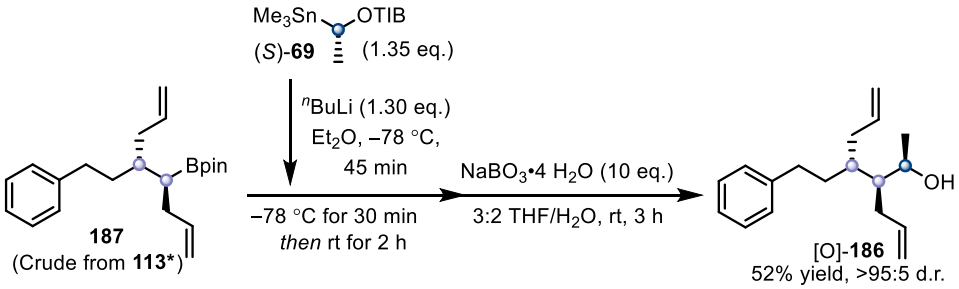
Table 19. Optimisation of the third homologation



Entry	*ent-syn*-**129b*** (eq.)	^{t}BuLi (eq.)	P:SM[a]	Yield (%)[b]	d.r.[c]
1	1.1	2.0	60:40	29	>95:5
2	1.5	2.0	76:24	34	>95:5
3	1.5	3.0	85:15	41	>95:5
4	2.0	3.5	85:15	39	>95:5

[a] Conversion to product determined by GCMS analysis of the reaction mixture
[b] Yields reported are those of isolated compound following by column chromatography (over the 4 steps)
[c] Diastereomeric ratios were determined by ^{13}C NMR analysis

Evidently, a major limitation of using α-sulfinyl benzoates as carbenoid precursors is the tendency of the reactive intermediate to undergo quenching pathways when the steric hindrance of the system is increased. Carbenoids generated from α-stannyl benzoates do not suffer from these side reactions and react *via* the desired homologation pathway even in very hindered environments. We therefore wondered whether α-stannyl benzoate (*S*)-**69** might provide [O]-**186** in higher yield. Indeed, upon performing the reaction, GCMS analysis indicated full conversion to product, which translated into a 52% yield of alcohol [O]-**186** over the 4 steps (85% yield per iteration) (Scheme 40). The high yield obtained with stannane (*S*)-**69** once again highlights the significance of the acidity of α-sulfinyl benzoates, and the sulfoxide-metal exchange by-product **172**, when attempting to homologate sterically hindered boronic esters.



Scheme 40. Homologation of **187** with the carbenoid derived from (*S*)-**69**

3.4. Conclusions

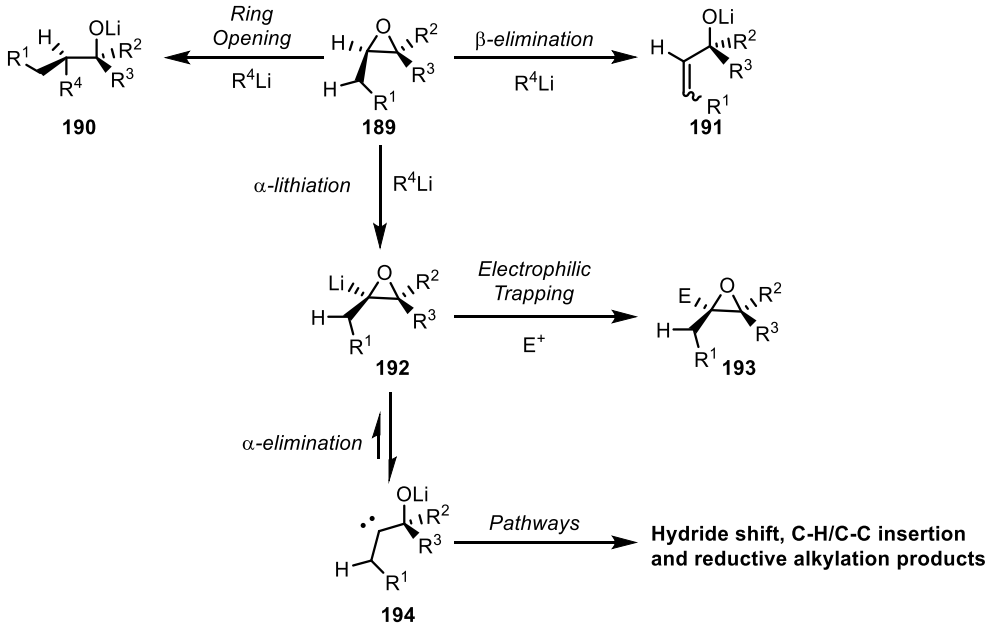
In summary, we have successfully demonstrated that α-sulfinyl benzoates can be employed as building blocks for the iterative homologation of boronic esters. This iterative process was found to deliver homologation product [O]-**186** in good yield and as a single stereoisomer. We have uncovered that carbenoids derived from α-sulfinyl benzoates are less competent in sterically hindered environments than those generated from α-stannyl benzoates, due to the occurrence of internal quenching pathways. However, the ability to prepare a library of these building blocks in highly enantioenriched form, and employ them as precursors to useful synthetic intermediates, will hopefully lead to their use by the wider scientific community.

4. Lithiated Epoxides for the Introduction of Hydroxyl Groups into Assembly–Line Synthesis

4.1. Introduction

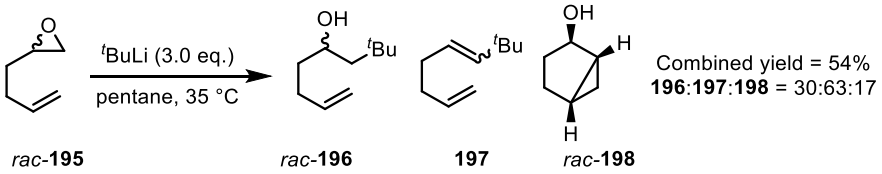
4.1.1. *Preparation and Transformations of Stabilised Lithiated Epoxides*

Lithiated epoxides have long been recognised as useful intermediates in organic synthesis owing to the range of transformations in which they participate (Scheme 41).[95]



Scheme 41. Pathways for the reaction of an epoxide with an organolithium reagent

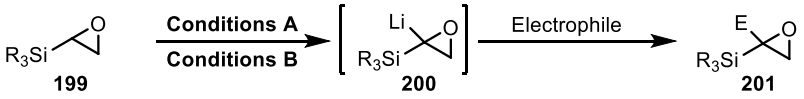
The reaction pathway is highly dependent on the nature of the substituents on the parent epoxide, which means that the reactions of lithiated epoxides are not always predictable and complex product mixtures can arise. For example, Crandall *et al.* reported that treatment of epoxide *rac*-**195** with ^{t}BuLi gave the products of ring opening (*rac*-**196**), reductive alkylation (**197**) and alkene insertion (*rac*-**198**) (Scheme 42).[96]



Scheme 42. Reaction of epoxide *rac*-**195** with ^{t}BuLi

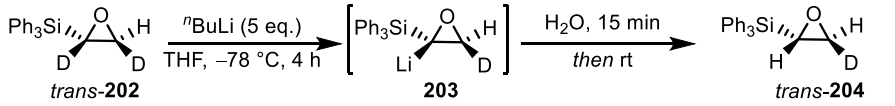
The reaction outcome becomes more predictable if anion stabilising groups are present on the epoxide starting material. Eisch and co-workers reported that a range of epoxysilanes could be lithiated upon treatment with ^{n}BuLi in THF at –78 °C, or ^{t}BuLi in pentane at –95 °C, and that resulting anion **200** could be quenched with D_2O, or trapped *in-situ* with TMSCl or $PhCONEt_2$ giving the corresponding products in high yields (Table 20).[97] The authors also showed that lithiation of epoxysilane *trans*-**202** and trapping with H_2O gave *trans*-epoxide **204** exclusively, demonstrating that lithiated species **203** is both chemically and configurationally stable under the reaction conditions. The scope of lithiated epoxides was investigated more thoroughly in a later study; it was found that benzylic, allylic and propargylic epoxides, as well as epoxyesters and epoxynitriles, could be lithiated at the α-position and subsequently trapped with a range of electrophiles to deliver a variety of substituted epoxides.[98]

Table 20. Lithiation and functionalisation of epoxysilanes

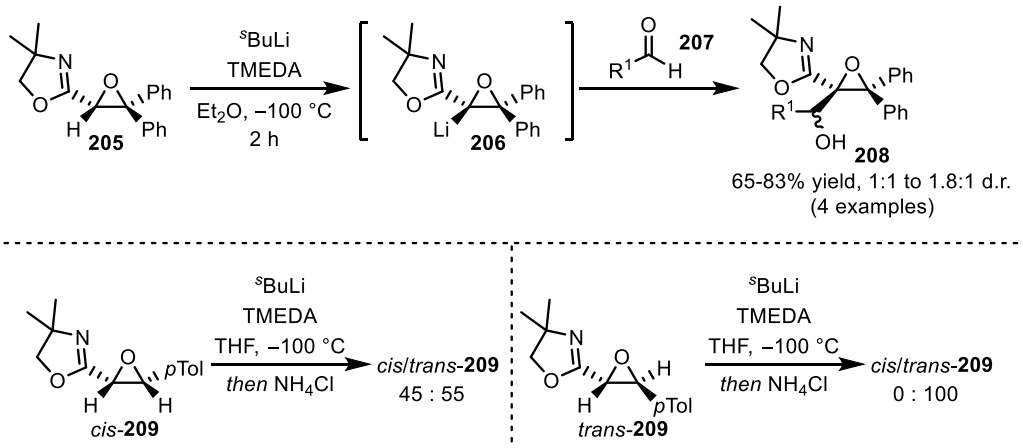


Conditions A: ^{t}BuLi (1.1 eq.), TMEDA (1.1 eq.), pentane, –95 °C,1 h
Conditions B: ^{n}BuLi (5.0 eq.), THF, –78 °C, 4 h

Entry	R	Conditions	Electrophile	Yield (%)
1	Me	A	TMSCl	75
2	Ph	A	$PhCONEt_2$	65
3	Ph	B	D_2O	~100

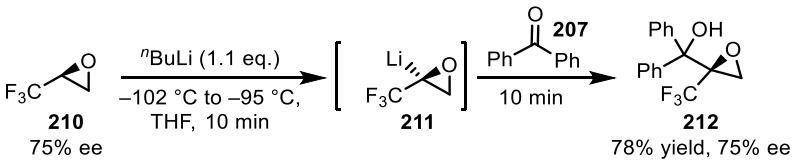


Florio and co-workers reported that the oxazolinyl moiety can be employed as the anion stabilising group.[99][100] They generated lithiated epoxide **206** by deprotonation of **205** with ^{s}BuLi at –100 °C and, after trapping with aldehydes **207**, tetrasubstituted epoxides such as **208** were formed in high yields (Scheme 43). They also demonstrated that lithiated oxazolinyl epoxides are not always configurationally stable. Epoxide *cis*-**209**, which was lithiated and quenched with ammonium chloride, delivered a diastereomeric mixture of **209** whereas, under the same conditions, epoxide *trans*-**209** gave exclusively the *trans*-product. The configurational lability of lithiated *cis*-epoxides is typically attributed to steric interactions between the *cis*-substituents.[95]



Scheme 43. Lithiation and functionalisation of oxazolinyl epoxide **205** and a configurational stability study

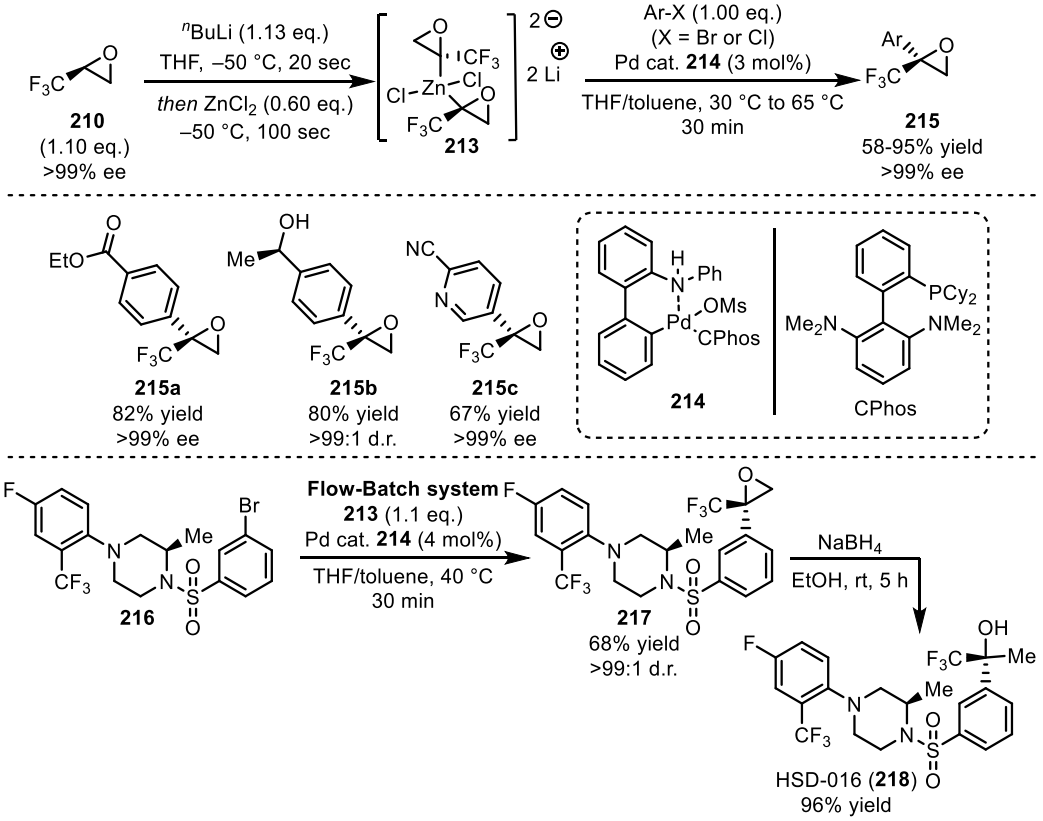
More recently, a trifluoromethyl substituent was used as an anion stabilising group to assist the lithiation of epoxides.[101] Uneyama and co-workers reported that chiral non-racemic (*S*)-trifluoromethylpropylene oxide (**210**) could be deprotonated at –102 °C with a slight excess of ^{n}BuLi and, upon trapping with ketone **207**, alcohol **212** was isolated in high yield and with complete retention of stereochemical integrity (Scheme 44). Evidently, defluorination pathways and other common side reactions are not in operation at this temperature. The authors found that the reaction could be performed at –78 °C with similar levels of efficiency (92% yield). However, at higher reaction temperatures (–40 °C) product **212** was not observed, which suggests that lithiated species **211** must not be chemically stable at this temperature and likely undergoes decomposition either through the elimination of fluoride or *via* the pathways outlined in Scheme 41. The authors subsequently demonstrated that lithiated epoxide **211** could be trapped with a variety of electrophiles at –102 °C to give, after ring-opening, pharmaceutically relevant enantioenriched alcohols bearing a trifluoromethyl substituent.



Scheme 44. Generation and trapping of a trifluoromethyl-stabilised lithiated epoxide

The group of Buchwald has utilised lithiated species **211** in cross-coupling reactions.[102] Epoxide **210** was prepared in enantiopure form through kinetic resolution of the racemate by employing Jacobsen's procedure.[103] Lithiated epoxide **211** was prepared in

continuous flow by deprotonation of **210** with ^{n}BuLi. **211** was then transmetallated, also in flow, with $ZnCl_2$ to form organozinc reagent **213** (Scheme 45). This compound was added in a batch process to a variety of different aryl halides and palladium catalyst **214** in THF/toluene, which delivered a range of cross-coupling products **215** in high yields and enantiomeric ratios. This flow-batch sequence was then applied to the preparation of HSD-016 (**218**), a drug candidate for the treatment of type-II diabetes.

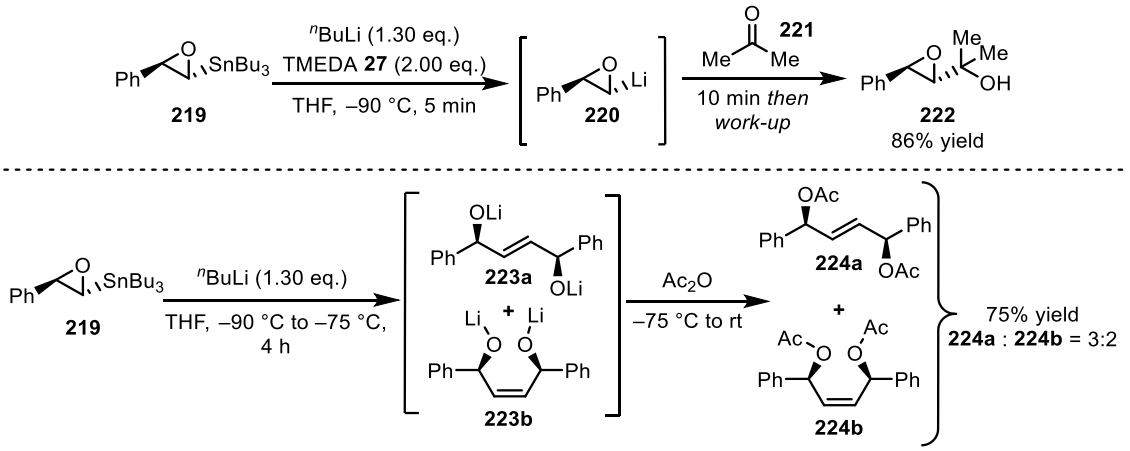


Scheme 45. Epoxide **210** for the preparation of enantioenriched organozinc reagent **213** and its use in Negishi coupling reactions

4.1.2. *Preparation and Transformations of non-Stabilised Lithiated Epoxides*

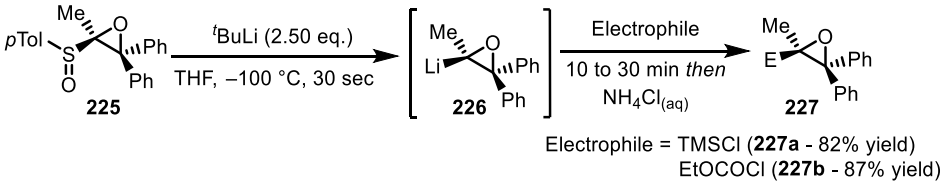
There have also been many reports regarding the formation and utilisation of non-stabilised lithiated epoxides. However, the lack of a stabilising group means that these carbenoids are prone to decomposition pathways and, as a result, need to be generated and reacted quickly at low temperature.[95] Pfaltz *et al.* demonstrated that such a procedure could be realised by using tin–lithium exchange to achieve rapid formation of non-stabilised organolithium **220**, which was shown to react with a variety of ketones with high fidelity (Scheme 46).[104] The authors found that TMEDA **27** was crucial to obtain the desired reactivity as performing the reaction in the absence of diamine resulted in

reductive alkylation products such as **224a** and **224b**. Presumably, the role of the diamine is to hinder the build-up of aggregates and suppress formation of the free carbene *via* α-elimination, which prevents the reductive alkylation pathway from taking place.



Scheme 46. Generation of lithiated epoxide **220** by tin–lithium exchange

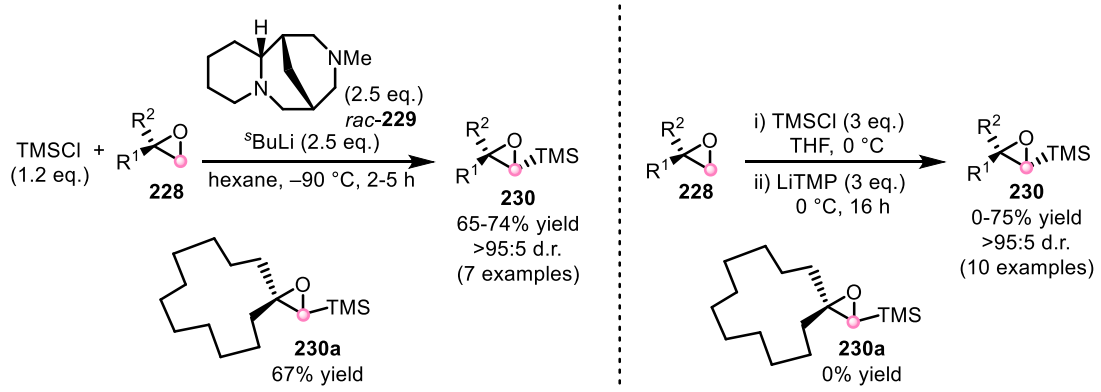
Similarly, sulfoxide–metal exchange has been used to prepare non-stabilised lithiated epoxides. Satoh *et al.* reported that a range of sulfinyl epoxides could be treated with ^{t}BuLi at –100 °C to rapidly generate lithiated epoxides species such as **226** (Scheme 47).[105] These lithiated epoxides were trapped with a variety of electrophiles in high yield.[106]



Scheme 47. Generation of non-stabilised lithiated epoxide **226** by sulfoxide–lithium exchange

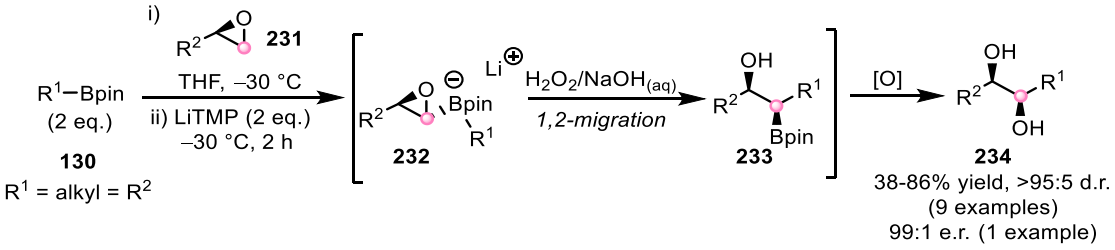
Non-stabilised lithiated epoxides have also been generated by deprotonation.[107] Hodgson and co-workers found that terminal epoxides **228** could be stereoselectively lithiated with ^{s}BuLi in the presence of diamine *rac*-**229** (Scheme 48).[108] The lithiated species was trapped *in-situ* with TMSCl to deliver synthetically valuable *trans*-substituted epoxysilanes **230** with excellent diastereoselectivity. The origin of the stereocontrol arises from the presence of the bulky diamine, which directs the lithiation to the least hindered face of the epoxide. Later studies from the Hodgson group revealed that the need for sterically encumbered diamines could be mitigated.[109] It was found that terminal

epoxides could be deprotonated in an efficient and stereoselective manner with lithium 2,2,6,6-tetramethylpiperide (LiTMP) which delivered, after *in-situ* trapping with TMSCl, similar products in comparable yields and diastereomeric ratios. However, it is notable that the diamine/^{s}BuLi protocol allowed isolation of product **230a** in good yield, whilst the method with LiTMP did not give any detectable amounts of epoxysilane **230a**.



Scheme 48. Generation of non-stabilised lithiated epoxides by deprotonation

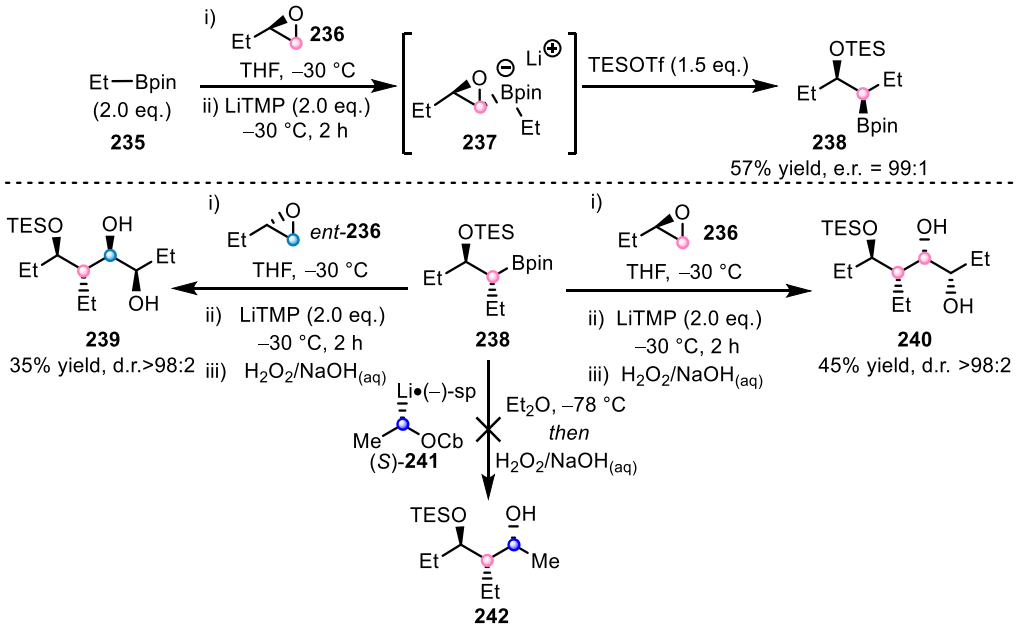
The scope of electrophiles for non-stabilised lithiated epoxides was further extended by Aggarwal and co-workers.[110] They showed that, through modification of the conditions developed by Hodgson *et al.*, TMSCl could be replaced with boronic ester **130** to give, after oxidative work-up, the corresponding *syn*-diol products **234** (Scheme 49). The mechanism was proposed to proceed by *in-situ* trapping of the *trans*-lithiated epoxide with boronic ester **130** to give boronate complex **232**. Upon treatment with $H_2O_2/NaOH_{(aq)}$ a 1,2-metallate rearrangement is triggered to give β-oxyboronic ester **233**, which is subsequently oxidised to diol **234**. When an enantioenriched epoxide was employed, the corresponding diol was obtained with no loss of stereochemical integrity.



Scheme 49. Homologation of boronic esters with non-stabilised lithiated epoxides

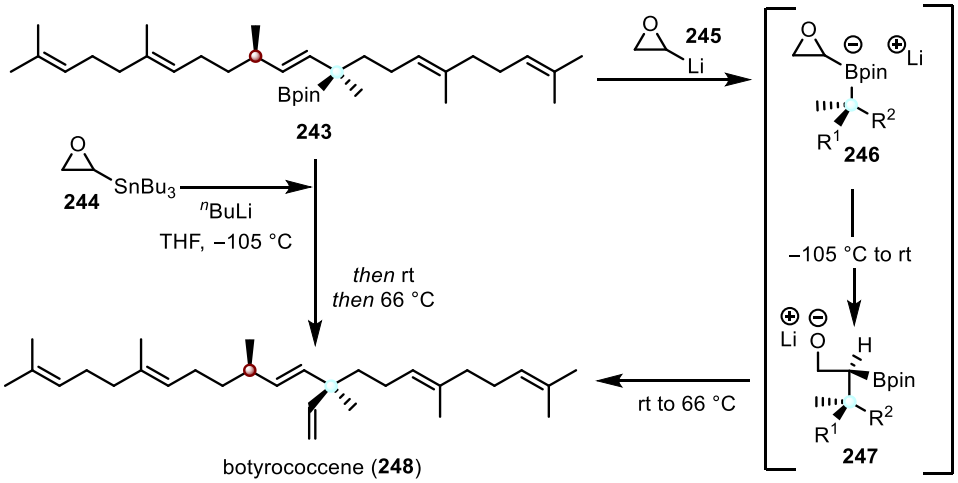
In the same report the authors showed that 1,2-migration could also be promoted with triethylsilyl triflate (TESOTf) (Scheme 50). This modified procedure gave β-oxyboronic ester **238** in good yield and as a single stereoisomer. This product was reacted with a

range of carbenoids to deliver a variety of valuable products.[111] However, reaction with lithiated carbamate (*S*)-**241** failed to deliver desired product **242**, which has since been attributed to the occurrence of a β-elimination pathway.[112]



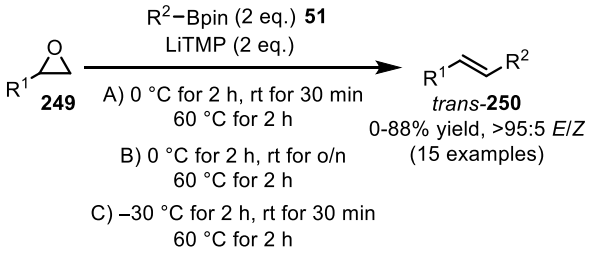
Scheme 50. Preparation and homologation of β-oxyboronic ester **238**

In a later study, Aggarwal *et al.* showed that the reaction of lithiated epoxides and boronic esters could be used to access alkene products (Scheme 51).[113] In their synthesis of botryococcene (**248**), the authors demonstrated that boronate complex **246**, generated from lithiated epoxide **245** and boronic ester **243**, underwent 1,2-migration upon warming to room temperature to give β-alkoxyboronate **247**, which participated in a boron-Wittig reaction under refluxing conditions to give the natural product botryococcene (**248**).



Scheme 51. Aggarwal's synthesis of botryococcene (**248**)

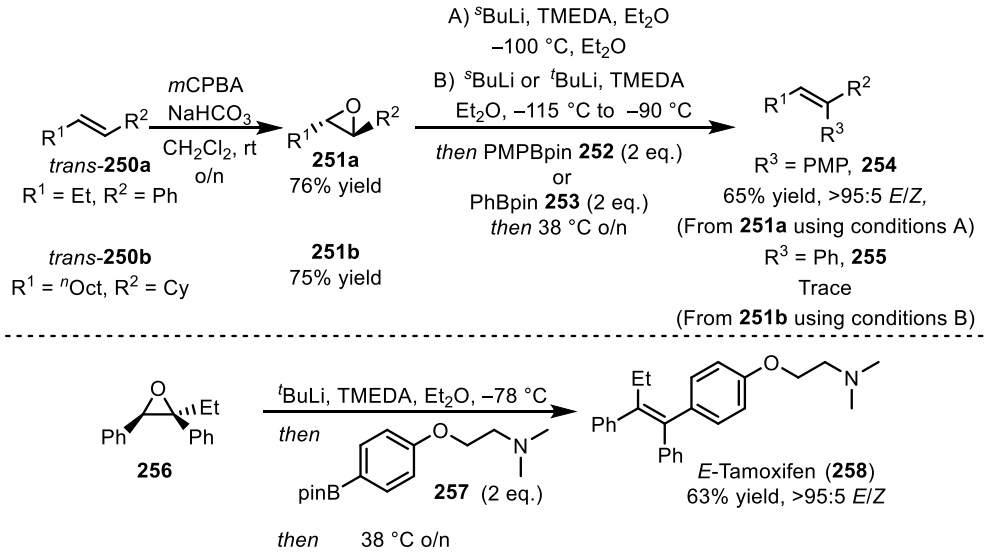
More recently, Hirschäuser and co-workers have extended this procedure to enable the stereoselective synthesis of substituted alkenes.[114] Terminal epoxides **249** were lithiated in the presence of boronic esters **51** and, after warming to room temperature and subsequently heating at reflux, the *trans*-alkene products *trans*-**250** were obtained in moderate to high yields as a single isomer (Scheme 52). Three sets of conditions were developed for the procedure. Conditions A were utilised for challenging lithiations, conditions B were used for boronic esters bearing groups that are slow to migrate and conditions C were used for epoxides derived from glycidol. A mechanism analogous to that described in Scheme 51 was proposed by the authors. The high stereoselectivity of the reaction can be explained by considering the following factors; LiTMP delivers exclusively the *trans* lithiated epoxide, the lithiated epoxide is configurationally stable and reacts with the boronic ester with retention of stereochemical information and the 1,2-migration and *syn*-elimination processes are completely stereospecific.



Scheme 52. Preparation of *trans*-disubstituted alkenes through an epoxide olefination reaction

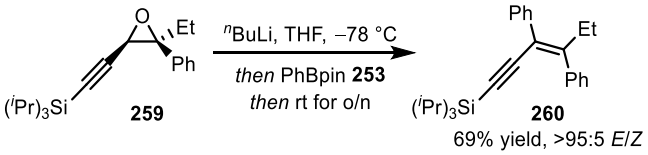
In the same report, Hirschäuser and co-workers demonstrated that the procedure could be rendered iterative by utilisation of the Prilezhaev reaction (Scheme 53).[115] Treatment of *trans*-**250a** with *meta*-chloroperbenzoic acid (*m*CPBA) delivered epoxide **251a** as a single diastereomer. Lithiation, using ^{s}BuLi and TMEDA (**27**) in Et_2O at –100 °C, followed by trapping with boronic ester **252** and heating gave trisubstituted alkene **254** in 65% yield and as a single isomer. However, the authors encountered a significant limitation of this methodology in that, for an effective lithiation, one of the substituents of the *trans*-disubstituted alkenes must be an aromatic group. For example, epoxide **251b** resisted lithiation at low temperature and, at higher temperatures, underwent decomposition. It seems that, for these challenging lithiations, it is important to have an anion stabilising group adjacent to the position of lithiation on the parent epoxide. Finally, the methodology was used to achieve an impressive synthesis of the anticancer drug

Tamoxifen (**258**), which was obtained in high yield and exclusively as the *E*-isomer following the reaction of epoxide **256** and boronic ester **257**.



Scheme 53. Lithiation-borylation-rearrangement-elimination of substituted epoxides and its application to the synthesis of Tamoxifen (**258**)

Pale and co-workers extended this lithiation-borylation-rearrangement-elimination procedure to ethynyloxiranes, which enabled the stereocontrolled synthesis of enynes (Scheme 54).[116] For example, ethynyloxirane **259** was lithated with ^{n}BuLi in THF at –78 °C, subsequent addition of boronic ester **253** followed by stirring at ambient temperature delivered enyne **260** in good yield.



Scheme 54. Stereocontrolled synthesis of enyne **260** from ethynyl oxirane **259**

4.2. Project Outline

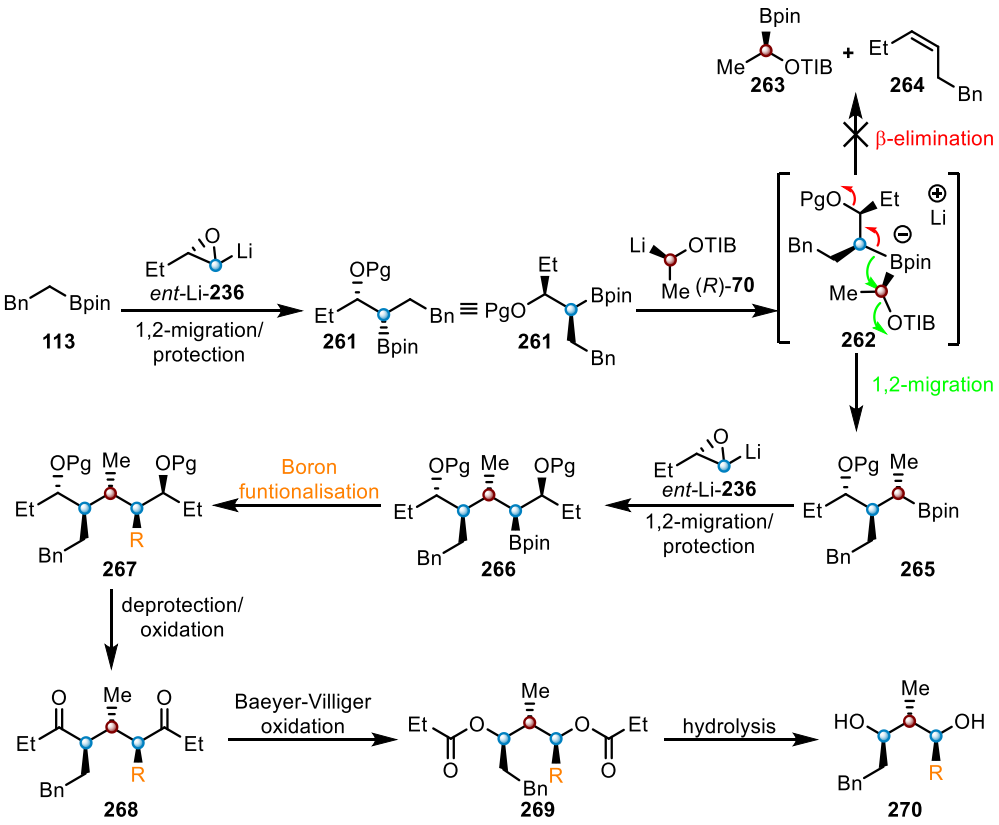
The aim of this project is to investigate the use of lithiated epoxides for the installation of hydroxyl groups into assembly–line synthesis. In section 1.2.2 (Scheme 17, page 13) an iterative homologation procedure that utilised lithiated α-chlorosilanes to achieve the same target transformation was described. Whilst elegant, this process is not ideal because:

- The method requires two steps per hydroxyl group (homologation reaction and photochemical cleavage of the pyrrolidine group).
- Extending the methodology to substrates of increased steric hindrance results in significant under-homologation and therefore reduced yields.
- Cleavage of the pyrrolidine side-arm results in a low atom economy for the overall process.

We therefore aim to develop a complementary procedure, which will be based on our group's earlier work (Scheme 49). We intend to modify and optimise the conditions for the reaction of lithiated epoxides and boronic esters to prepare β-alkoxy boronic esters. Once optimised, the lithiation–borylation method will be applied iteratively towards the preparation of a polypropionate motif, which will give an indication of whether this building block can serve as a suitable alternative to lithiated α-chlorosilanes.

The route towards polypropionate **270** is outlined below (Scheme 55). Firstly, treatment of starting boronic ester **113**, which must be the limiting reagent, with lithiated epoxide *ent*-Li-**236** and a 1,2-migration promoter will give β-oxyboronic ester **261**. Next, we hope that reaction of **261** with lithiated TIB ester (*R*)-**70** will give boronic ester **265**. This step will be a significant challenge for this project, as it is well known that a common reaction pathway of boronate complexes of type **262** is β-elimination.[112] However, we have already established that benzoates are better leaving groups than carbamates (Table 2, page 10) and previous work from our group indicates that, for boronate **262**, the desired 1,2-migration pathway might be favoured over β-elimination.[117] A second homologation with lithiated epoxide *ent*-Li-**236** should give boronic ester **266**, which would then be subject to a boron functionalisation reaction to give **267**. Next, a global deprotection–oxidation sequence would be performed to give diketone **268** which, upon treatment with *m*CPBA, should undergo a poly-Baeyer-Villiger oxidation to give diester **269**.[118] The

carbon backbone will migrate preferentially as it is better able to accommodate the build-up of positive charge in the reaction transition-state compared to the ethyl group. Importantly, the migration step is known to be stereospecific and proceeds with retention of configuration, which means the product should be obtained as a single stereoisomer. Compound **269** will then be subject to hydrolysis to give desired polypropionate **270**.



Scheme 55. Proposed route to polypropionate **270**

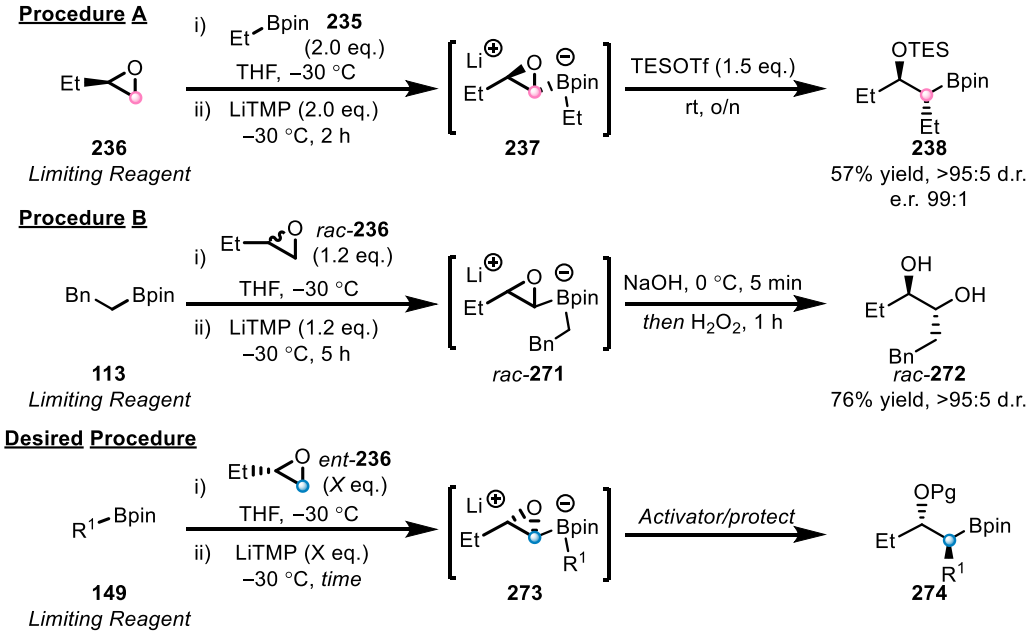
The potential advantages of using this lithiated epoxide strategy rather than the lithiated α-chlorosilane building block are:

- The lithiated epoxide is relatively unhindered when compared to lithiated α-chlorosilane **77**, so the reaction should work well with hindered boronic esters.
- A global deprotection–oxidation step is performed at the end of the synthesis, rather than a photochemical oxidative cleavage step after each homologation, thus reducing the number of manipulations. This is particularly true for assembly–line processes involving multiple homologations with lithiated epoxides.

4.3. Results & Discussion

4.3.1. *Reaction Optimisation*

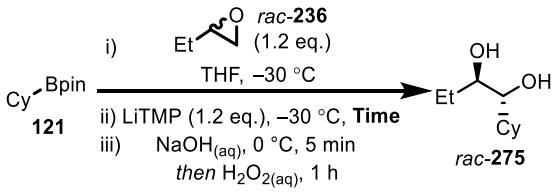
As a starting point, we considered the conditions that had been previously used for the reaction of lithiated epoxide Li-**236** and boronic esters (Scheme 50, page 51). It was outlined earlier that the reaction to give β-oxyboronic ester **238** employed an excess of the starting boronic ester **235**, a characteristic that is not compatible with assembly–line synthesis (Procedure A, Scheme 56).[110] This issue has since been addressed by our group and it was found that diol **272** could be obtained in high yield when boronic ester **113** was used as the limiting reagent (Procedure B).[119] We therefore looked to amalgamate procedures A and B to realise a method that both provides access to ß-oxyboronic ester **274** and employs starting boronic ester **149** as the limiting reagent.



Scheme 56. Comparison of past procedures and the desired procedure for the reaction of boronic esters and lithiated epoxide *ent*-Li-**236**

We first looked to address the reaction time of Procedure B as we believed that a period of five hours at –30 °C lacked the practicality required for an assembly–line protocol (Table 21). Using cyclohexyl boronic ester **121**, it was found that performing the reaction for 2 h (Entry 3) achieved a similar yield to when the reaction was stirred for 5 h (Entry 4). We therefore elected to take these conditions forward for further optimisation.

Table 21. Optimisation of the lithiation–borylation time for the reaction of boronic ester **121** and lithiated epoxide *rac*-Li-**236**

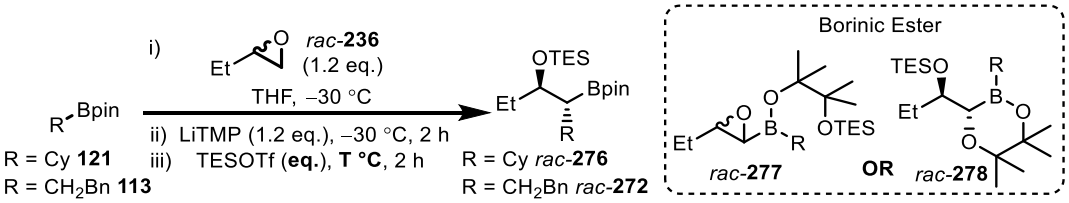


Entry	Time (h)	Yield **275** (%)[a]
1	0.25	56
2	1	64
3	2	70 (69%)
4	5	76

[a] Corresponds to NMR yield using 1,3,5-trimethoxybenzene as an internal standard, isolated yields are reported in parentheses.

We next focused our efforts towards the synthesis of β-oxyboronic esters *rac*-**276** and *rac*-**272** (Table 22). We attempted to use TESOTf to promote 1,2-migration, however all efforts were met with low yields and the formation of considerable amounts of borinic ester, which was observed by ^{11}B NMR (2). The structure of the borinic ester is likely to be either *rac*-**277** or *rac*-**278**, however neither compound could be isolated, which was attributed to the inherent instability of these compounds.[120] Using primary boronic ester **113**, we attempted to negate the formation of this side product by addition of TESOTf at lower temperature and in reduced quantities (Entries 2 and 3), however no improvement in yield was observed.

Table 22. Use of TESOTf to promote 1,2-migration



Entry	R =	TESOTf (eq.)	Temperature (°C)	Boronic ester: Borinic ester[a]	Yield **276**/**272** (%)[b]
1	Cy	1.5	–30 to rt	61:29	57 (46)
2	CH_2Bn	1.5	–78 to rt	ND	- (50)
3	CH_2Bn	1.1	–78 to rt	ND	55

[a] Ratio determined by ^{11}B NMR conversion
[b] Corresponds to NMR yield using 1,3,5-trimethoxybenzene as internal standard, isolated yields are reported in parentheses

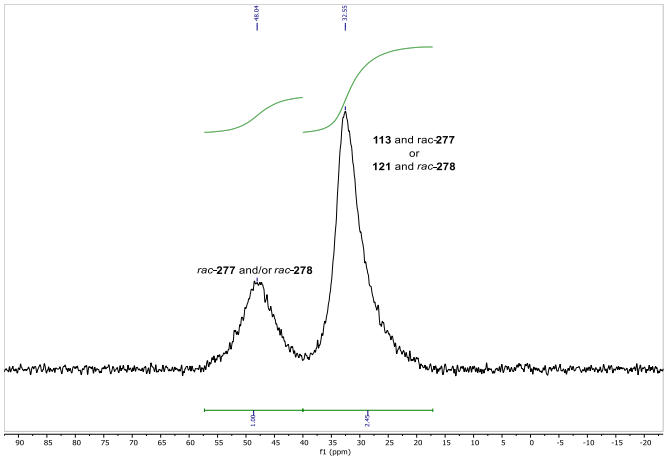
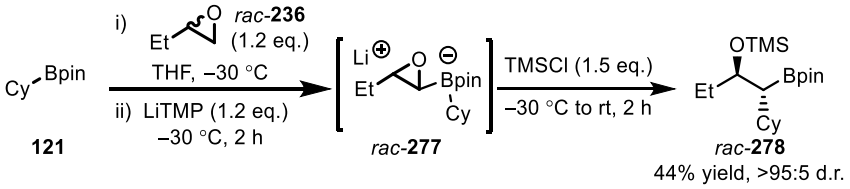


Figure 2. ^{11}B NMR for the reaction of boronate complex, derived from **121** and *rac*-Li-**236**, with TESOTf (Table 22, Entry 1)

Having previously observed a 76% yield for diol *rac*-**275** (Table 21, Entry 4), we were keen to investigate whether the yield of β-oxyboronic ester could be improved. We thought that TMSCl might serve as a milder alternative to TESOTf for the promotion of 1,2-migration, which should lead to reduced amounts of borinic ester (Scheme 57). Upon treatment of boronate complex *rac*-**277** with TMSCl at low temperature, only boronic ester was observed by ^{11}B NMR (Figure 3). However, desired product *rac*-**278** was obtained in just 44% yield and starting material **121** was observed as a major species.



Scheme 57. Use of TMSCl to promote 1,2-migration

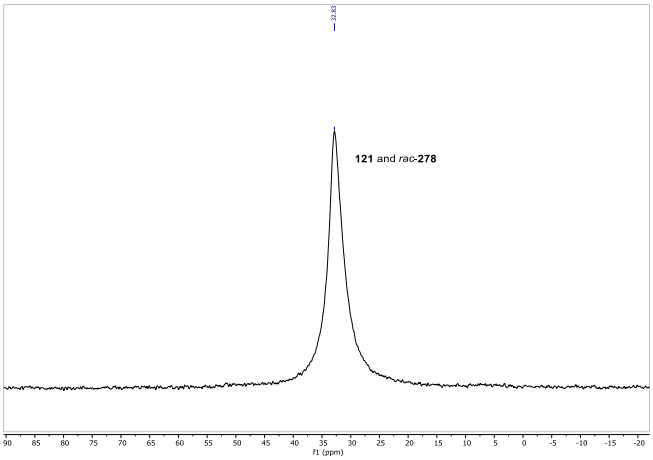
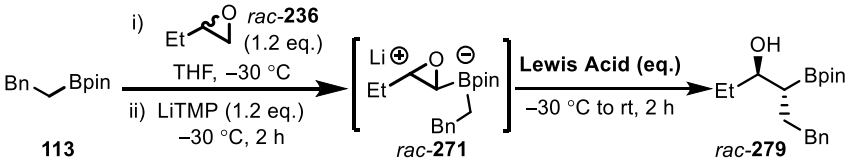


Figure 3. ^{11}B NMR for the reaction of boronate complex *rac*-**277** with TMSCl

Having been unable to reproduce the yields achieved for the preparation of diol *rac*-**275**, we investigated different 1,2-migration promoters (Table 23). We considered the possibility of accessing a β-oxyboronic ester of type **274** *via* protection of the intermediate β-hydroxyboronic ester *rac*-**279**, which led us to screen a variety of Lewis acids. Addition of $Sc(OTf)_3$ (Entry 1) and $FeCl_3$ (Entry 2) to boronate complex *rac*-**271** at –30 °C resulted in messy reactions that resulted in low yields of *rac*-**279**. Interestingly, it was found that addition of $CeCl_3$, LiOTf, $ZnCl_2$, $MgBr_2$ and $MgBr_2$•MeOH (Entries 3-7) all gave similar levels of reaction success, which allowed isolation of the desired product *rac*-**279** in a pleasing 68% yield; starting boronic ester **113** was apparent in all cases. The optimal reagent for promoting 1,2-migration was identified as $MgBr_2$•MeOH owing to ease of handling.

Table 23. Lewis acid screen

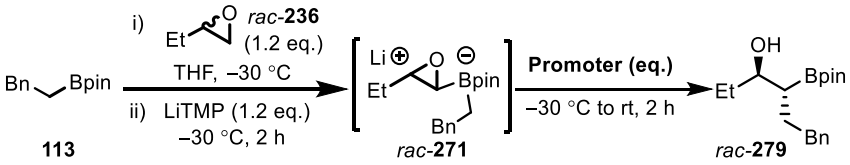


Entry	Lewis acid (eq.)	Yield **279** / **113**[a]
1	$Sc(OTf)_3$ (1.4)	45% / 25%
2	$FeCl_3$ (1.4)	40% / 23%
3	$CeCl_3$ (1.4)	71% / 25%
4	LiOTf (1.4)	69% / 18%
5	$ZnCl_2$ (1.4)	68% / 20%
6	$MgBr_2$ (1.4)	68% / 22%
7	$MgBr_2$•MeOH (1.5)[b]	69% (68%) / 22%

[a] Corresponds to NMR yield using 1,3,5-trimethoxybenzene as internal standard, isolated yields are reported in parentheses
[b] A 1 M solution of $MgBr_2$•MeOH was used

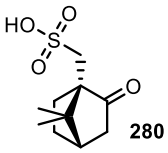
A variety of other conditions for promoting 1,2-migration were also investigated (Table 24). Brønsted acids (Entries 1-4) gave the desired product in reasonable yield, as did hydrogen bond donors (Entries 5-6), however no improvement on the result obtained with $MgBr_2$•MeOH was achieved.

Table 24. A screen of 1,2-migration promoters

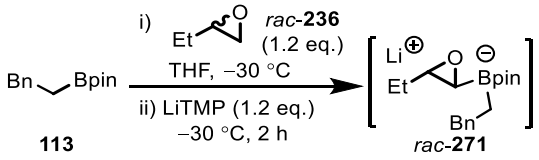


Entry	Promoter (eq.)	Yield **279** / **113** (%)[a]
1	$NH_4Cl_{(aq)}$ (*exc.*)	50% / N.D.
2	AcOH (2.0)	60% / 20%
3	TsOH•H_2O (1.2)	54% / 27%
4	**280** (1.2)	62% / 37%
5	H_2O (*exc.*)	57% / N.D.
6	MeOH (2.0)	64% / N.D.

[a] Corresponds to NMR yield using 1,3,5-trimethoxybenzene as internal standard



We were intrigued as to why the conversion of starting boronic ester **113** to product *rac*-**279** was so similar for several different 1,2-migration promoters (Table 23, Entries 3-7). We thought that perhaps we were unable to achieve complete formation of boronate complex *rac*-**271** under the reaction conditions. Therefore, we attempted to measure the degree of boronate complex formation for our optimised procedure (Figure 4). After treating a mixture of boronic ester **113** and epoxide *rac*-**236** at low temperature with LiTMP, a sample was taken and analysed by ^{11}B NMR spectroscopy. A small signal at 33 ppm indicated that a trace amount of starting boronic ester **113** remained and the presence of a large broad signal at ~8 ppm confirmed formation of a boronate complex.



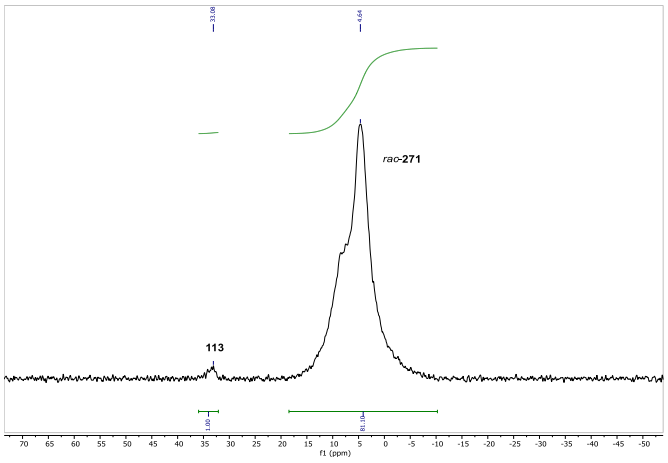


Figure 4. ^{11}B NMR for the reaction of boronic ester **113**, epoxide *rac*-**236** and LiTMP

As a control experiment, the same study was performed in the absence of epoxide *rac*-**236** (Figure 5). Curiously, a peak corresponding to boronate complex was also observed. Evidently, at room temperature, LiTMP, or a decomposition product thereof, is capable of forming a boronate complex. This study elucidated that it would not be possible to accurately monitor the formation of boronate complex *rac*-**271** by ^{11}B NMR analysis.

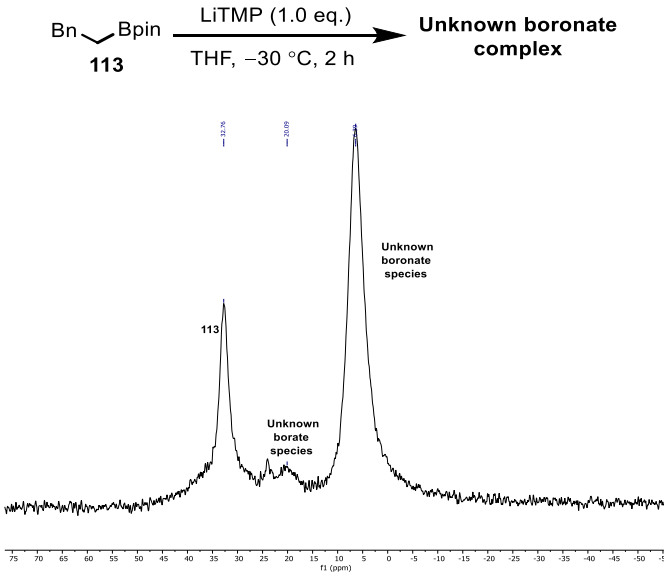
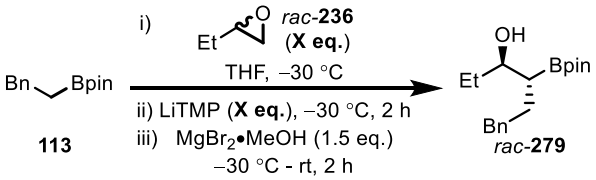


Figure 5. ^{11}B NMR for the reaction of boronic ester **113** and LiTMP

We decided to investigate the effect of varying the equivalents of epoxide *rac*-**236** and LiTMP on reaction success (Table 25), as a means to investigate the levels of boronate complex formation. Interestingly, increasing the equivalents of both the epoxide and LiTMP had a negligible effect on the reaction outcome. Likewise, performing the reaction with a large excess of the epoxide with respect to both boronic ester **113** and LiTMP did not lead to an improved reaction. This latter experiment (Entry 3) was anticipated to improve the yield of the reaction should boronic ester **113** and LiTMP react at –30 °C.

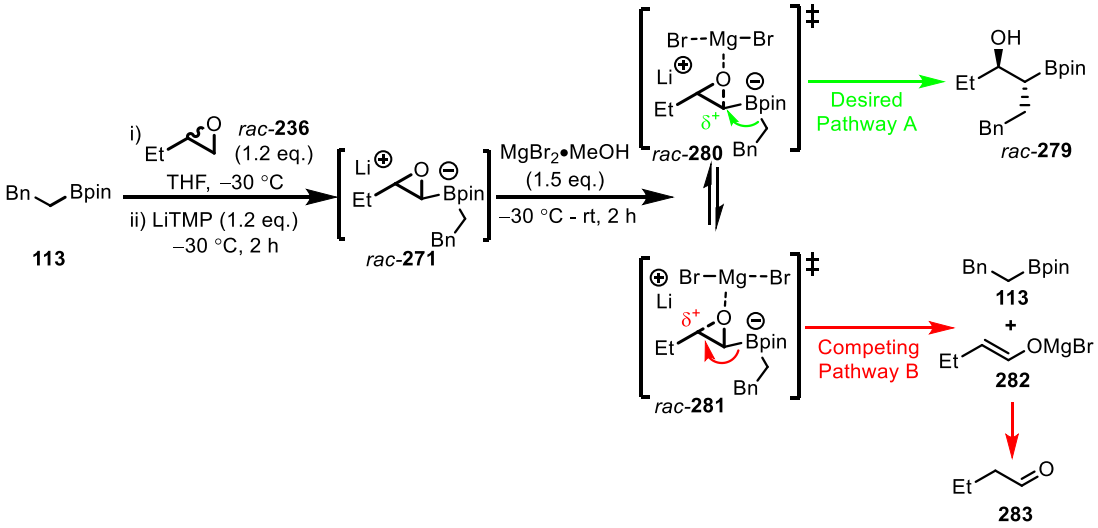
Table 25. Variation of the equivalents of epoxide *rac*-**236** and LiTMP



Entry	Epoxide (eq.)	LiTMP (eq.)	Yield **279**[a]
1	1.2	1.2	68%
2	2.0	2.0	65%
3	5.0	1.2	68%

[a] Corresponds to NMR yield using 1,3,5-trimethoxybenzene as internal standard

These results suggested that incomplete formation of boronate *rac*-**271** was not the factor leading to the limited reaction success as increasing the amounts of lithiated species had not improved the yield of reaction. Based on this study, and the results of the Lewis acid screen (Table 23), we hypothesised that an equilibrium might be reached upon addition of the 1,2-migration promoter (Scheme 58). If one considers Pathway A, upon addition of $MgBr_2$•MeOH to the reaction there is a build-up of positive charge on the carbon adjacent to boron in transition-state *rac*-**280**, which subsequently results in 1,2-migration and desired product *rac*-**279**. Alternatively, if we consider pathway B the positive charge build-up is placed on the carbon adjacent to the ethyl group, resulting in a pathway that returns starting boronic ester **113**. Whilst we expected that the boronate substituent would better stabilise positive charge relative to an ethyl group, it is possible that both pathways are in operation, which would explain why starting boronic ester **113** was often present in the crude reaction mixture (Table 23). It should be noted that we did not observe the presence of butanal (**283**) by ^{1}H NMR analysis.



Scheme 58. Possible reaction pathways upon addition of $MgBr_2$•MeOH to boronate complex *rac*-**271**

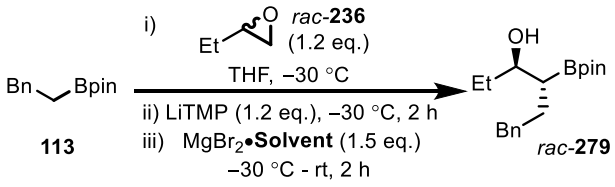
Note: It has already been discussed that MeOH can also promote 1,2-migration, however this was omitted from this scheme for clarity

Whilst we had no evidence that build-up of positive charge in the transition state was an important factor in determining the reaction pathway, we decided to investigate the addition of $MgBr_2$ in solvents of varying polarity, in an attempt to probe our hypothesis and increase the yield of the reaction (Table 26). Addition of $MgBr_2$ in THF, dielectric

constant (ε) = 7.5 Faraday / M, gave a similar yield to our previous result with $MgBr_2$ in MeOH, dielectric constant (ε) = 32.6 Faraday / M, which suggested that our hypothesis was not valid. Performing the reaction in toluene, which is a significantly less polar solvent than both THF and MeOH, resulted in a slight decrease in yield and a messy reaction. Addition of $MgBr_2$ in acetonitrile led to a variety of side-products, which prevented the quantities of product *rac*-**279** and starting material **113** from being determined by ^1H NMR analysis of the crude reaction mixture.

Table 26. Variation of solvent polarity for 1,2-migration

Note: Values for dielectric constants were abstracted from Vogel's Textbook of Practical Organic Chemistry[121]

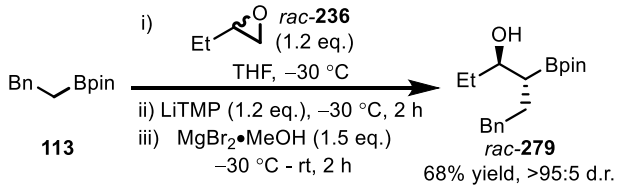


Entry	Solvent[a]	Dielectric Constant (F / m)	Yield **279** / **113**[b]
1	MeOH	32.6	69% / 23%
2	THF	7.5	68% / 22%
3	DMF	38.3	68% / 19%
4	Toluene	2.4	46% / 23%
5	Acetonitrile	36.6	N.D. / N.D.

[a] Reaction mixtures of boronate *rac*-**271** were added dropwise to a vial containing $MgBr_2$ and the specified solvent

[b] Corresponds to NMR yield using 1,3,5-trimethoxybenzene as internal standard

It remains ambiguous as to why full conversion of starting material **113** to product *rac*-**279** cannot be achieved. However, having invested considerable time into the optimisation of the reaction (Scheme 59), we decided to proceed with the iterative study towards polypropionate motif **270**.

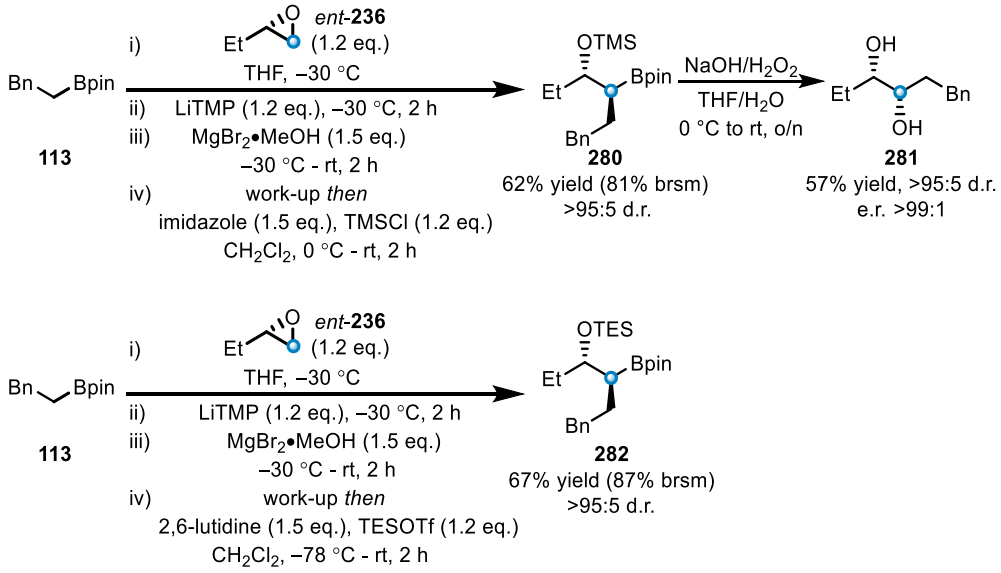


Scheme 59. Optimised conditions for the homologation of boronic ester with lithiated epoxide *rac*-Li-**236**

4.3.2. *Iterative Study Towards Polypropionate Motif* **270**

Having developed conditions for the lithiation–borylation reaction between boronic ester **113** and lithiated epoxide *rac*-Li-**236**, we were keen to investigate whether these new conditions could be applied in an iterative fashion towards **270** (Scheme 55, page 55).

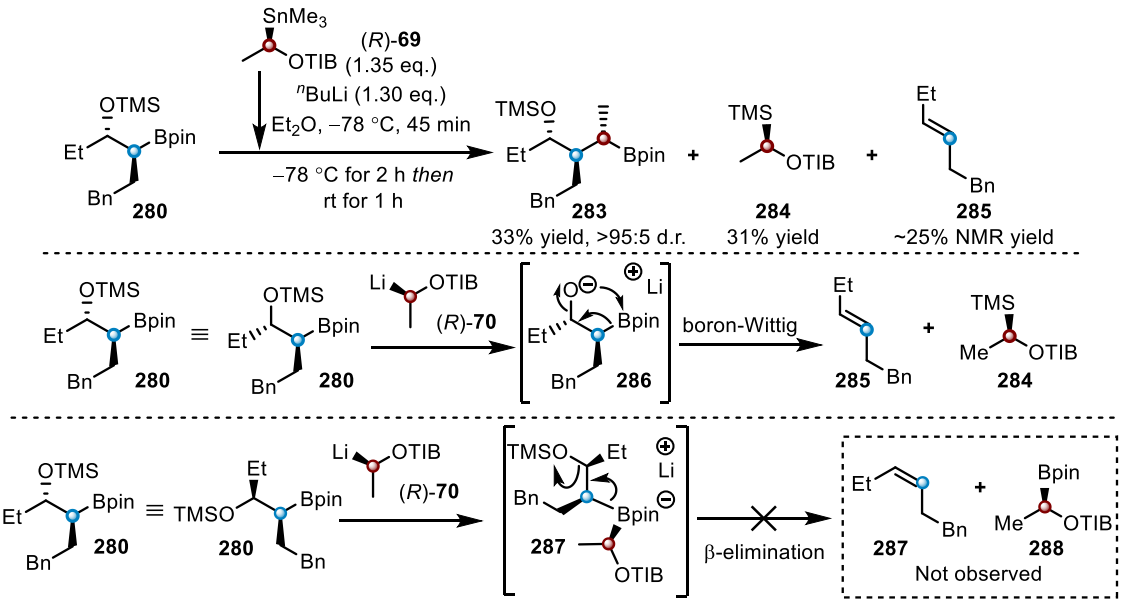
We first needed to identify a suitable hydroxyl protecting group to install following the homologation reaction. We reasoned that a silyl ether would offer the ideal balance between tolerance towards organolithium reagents, tuneable steric hindrance and ease of removal. When considering how to install the protecting group, we were wary of having to perform multiple purification procedures, as this would not be time efficient or in-keeping with the principles of assembly–line synthesis. At the same time, we did not believe that a one-pot process for lithiation–borylation, 1.2-migration and protection would be possible, owing to the excess of methanol present in the reaction mixture. Therefore, we elected to protect the hydroxyl group following an intermediary aqueous work-up procedure (Scheme 60). We were pleased to find that both trimethylsilyl (TMS) and triethylsilyl (TES) protecting groups could be installed with a minimal impact on reaction yield. As anticipated, when enantioenriched epoxide *ent*-**236** was used, β-alkoxyboronic ester **280** was found to be enantiopure, which was determined by chiral HPLC analysis of diol **281**.



Scheme 60. Preparation of enantioenriched β-oxyboronic esters **280** and **282**

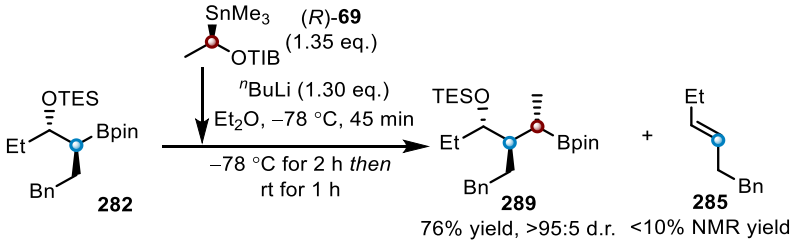
The next step was to investigate a key aspect of the project, homologation of β-oxyboronic esters **280** and **282** with lithiated benzoate (*R*)-**70** (Scheme 61). For this reaction we

elected to use conditions previously developed within our group.[70] Upon reaction of β-oxyboronic ester **280** with (*R*)-**70**, generated *ex-situ* from (*R*)-**69** by tin–lithium exchange, desired product **283** was isolated in a disappointing 33% yield. α-Silyl benzoate **284** was also obtained and alkene **285** was observed by ^{1}H NMR analysis of the crude reaction mixture. Evidently, the lithiated species removes the trimethylsilyl protecting group to give β-alkoxyboronic ester **286**, which then undergoes a boron-Wittig reaction to give *trans*-alkene **285**. Encouragingly, there was no evidence of any β-elimination pathway, as neither **287** nor **288** were observed.



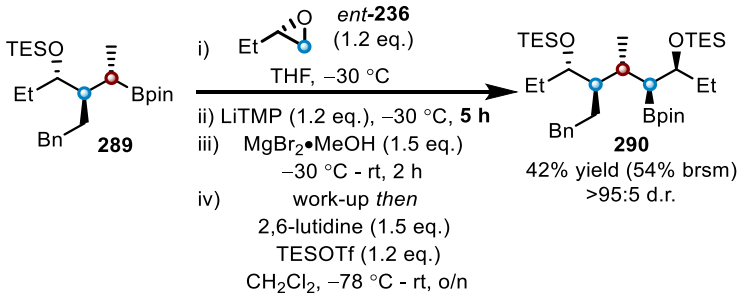
Scheme 61. Reaction of β-oxyboronic ester **280** and lithiated TIB ester (*R*)-**70**

Fortunately, the more hindered TES group meant that **282** was more resistant towards desilylation and, under the same reaction conditions, desired product **289** was isolated in a gratifying 76% yield (Scheme 62). While we did observe side-product **285** in trace amounts, the decision was taken to proceed to the next step.



Scheme 62. Reaction of β-oxyboronic ester **282** and lithiated TIB ester (*R*)-**70**

We turned our attention to the third stage of the sequence, reaction of boronic ester **289** and lithiated epoxide *ent*-Li-**236** (Scheme 63). The procedure was modified slightly from the optimised conditions; due to the hindered nature of boronic ester **289**, we elected to increase the period for lithiation–borylation to 5 h to give the reaction an improved chance of success. ^{11}B NMR analysis of the reaction mixture indicated that after this time only 80% conversion to a boronate complex was achieved (Figure 6). Despite our initial view that the reactivity of lithiated epoxide *ent*-Li-**236** should be reasonably insensitive to steric hindrance, it appeared that using a more encumbered starting boronic ester resulted in a less efficient reaction. After treatment with $MgBr_2$•MeOH and subsequent protection, desired product **290** was isolated in a disappointing 42% yield.



Scheme 63. Reaction of boronic ester **289** and lithiated epoxide *ent*-Li-**236**

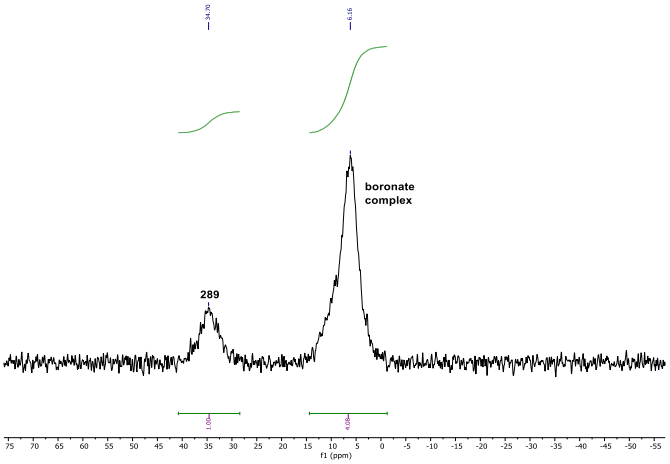


Figure 6. ^{11}B NMR for the reaction of boronic ester **289**, epoxide *ent*-**236**, and LiTMP
Note: Taken prior to the addition of $MgBr_2$•MeOH

At this point we were concerned with several aspects of the project. Firstly, for primary boronic ester **113** we were unable to optimise the reaction beyond 70% conversion. This did not meet the requirements of an assembly–line protocol, which demands that high levels of conversion are achieved in order to avoid intermediary purification where

possible. More significantly, contrary to our initial hypothesis it seemed that the reaction of lithiated epoxide *ent*-Li-**236** with boronic esters is sensitive to steric hindrance, which resulted in a low yield of **290** for the final homologation. Moreover, during this project it became clear that β–oxyboronic esters **280**, **282** and **290** are quite unstable, which made their handling challenging. At this point, it was apparent that our proposed lithiated epoxide strategy would not be a superior method to the lithiated α-chlorosilane approach for the stereoselective installation of hydroxyl groups into assembly–line synthesis. As a result, the decision was taken to abandon the project at this stage.

4.4. Conclusions

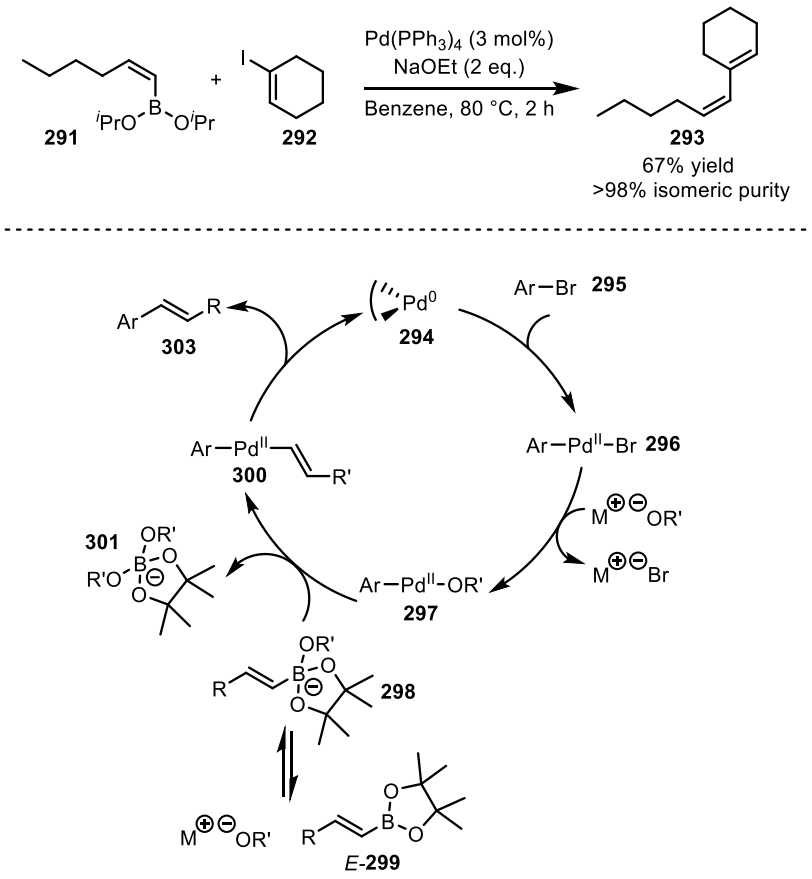
A reproducible procedure to prepare stereopure β-oxyboronic esters in good yields from the reaction of a lithiated epoxide and boronic ester has been realised. It was found that lithiated TIB ester (*R*)-**70** efficiently homologated ß-oxyboronic ester **282**, with no evidence of β-elimination, a pathway that is prevalent for the corresponding reaction with lithiated carbamates. An assembly–line strategy, that employed lithiated epoxide *ent*-Li-**236** and lithiated TIB ester (*R*)-**70** to prepare polypropionate motif **270** was investigated. However, this approach was deemed less efficient than the method that uses lithiated α-chlorosilane building blocks, which led to discontinuation of this project.

5. Vinylidene Homologation of Boronic Esters and its Application to the Synthesis and Structural Revision of Machillene

5.1. Introduction

5.1.1. *Vinyl Boronic Esters as Versatile Synthetic Intermediates*

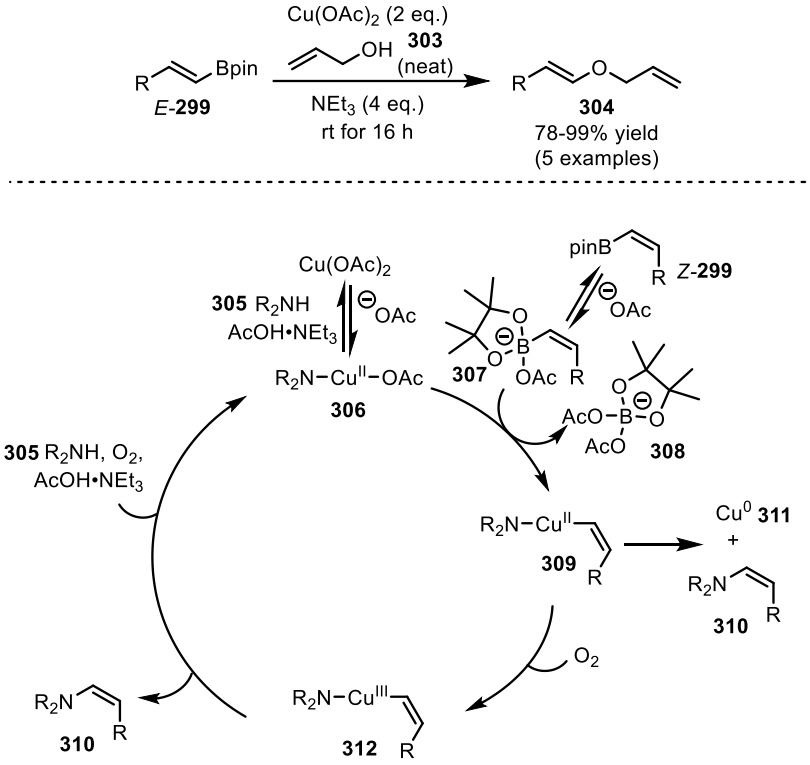
Over the last 50 years, vinyl boronic esters have emerged as valuable reagents for synthetic chemists.[122] The most notable development that has resulted in the widespread use of these reagents is the ascension of transition-metal catalysis.[123] Specifically, the Suzuki-Miyaura cross-coupling reaction, which involves the palladium-catalysed coupling of an organohalide, such as **292**, and organoboronic ester, such as **291**, has revolutionised modern synthetic chemistry (Scheme 64).[124-125] A typical example of a catalytic cycle for the Suzuki reaction of an aryl bromide and alkenyl pinacol boronic ester is shown below. Oxidative addition of Pd^0 catalyst **294** into the C–Br bond of **295** gives Pd^{II} intermediate **296**, which undergoes a ligand transfer with a molecule of base to give **297**. Transmetallation of **297** with vinyl boronate **298**, which is formed by the co-ordination of base to boronic ester *E*-**299**, leads to intermediate **300**. The final step of the cycle is reductive elimination, which delivers coupling product **302** and regenerates catalyst **294**. While the initial work of Suzuki and co-workers was focused on forming C-C bonds between sp^2-hybridised carbon centres, recent developments in this field has meant that coupling of even the most complex fragments can be achieved.[126] The efficiency and reliability of the Suzuki-Miyaura coupling has been recognised by chemical industries and, consequently, it has become one of the most frequently utilised reactions in the discovery and production of drug and agrochemical compounds.[127]



Scheme 64. The Suzuki-Miyaura cross-coupling reaction

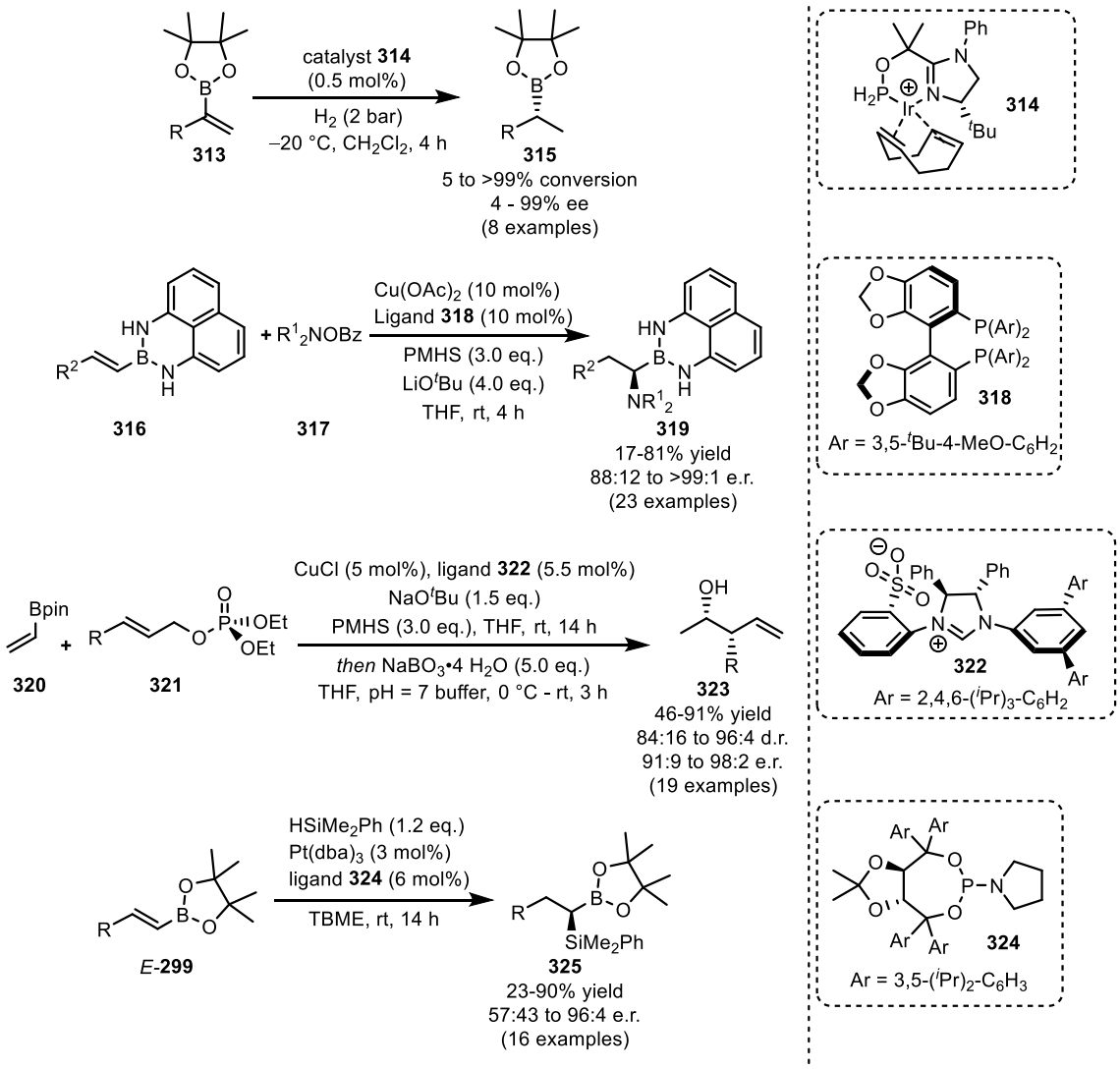
Vinyl boronic esters have also been employed in other transition-metal catalysed processes. Chan, Lam and co-workers have reported the coupling of vinyl and aryl boronic acids with alcohols and amines under copper catalysis to give the corresponding enol/enamine products.[128-130] The scope of this methodology was expanded to include vinyl boronic esters by Merlic and co-workers, who showed that vinyl boronic esters *E*-**299** could be coupled with allylic alcohol **303** in the presence of stoichiometric copper (II) acetate to give the corresponding products **304** in excellent yields (Scheme 65). A general catalytic cycle for the Chan-Lam coupling of an amine **305** and vinyl boronic ester *Z*-**299** is displayed below. [131] The catalytic cycle commences with a copper assisted deprotonation of amine **305** to give intermediate **306**, which undergoes transmetallation with vinylboronate **307** to generate Cu^{II} species **309**. This intermediate can either undergo a slow reductive elimination, which delivers coupling product **310** and Cu^{0} species **311**, or be oxidised by molecular oxygen to give **312**. The Cu^{III} species **312** undergoes a more efficient reductive elimination, relative to **309**, and is thus the most likely intermediate on route to product **310.** Following reductive elimination, oxidation of the resulting Cu^{I} species regenerates active catalyst **306**. Typically, Chan-Lam coupling reactions are

performed under an atmosphere of oxygen to enhance the rate of reaction. Since the pioneering work of Chan and Lam, countless variations of this transformation have been reported and now most carbon heteroatom bonds can be formed using this methodology.[132]



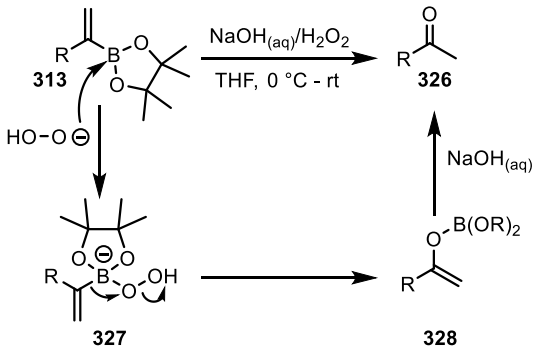
Scheme 65. The Chan-Lam coupling reaction

A useful strategy for the synthesis of chiral non-racemic boronic esters is the enantioselective hydrofunctionalisation of vinyl boronic esters (Scheme 66). Methods for asymmetric hydrogenation,[133] hydroamination,[134] hydroallylation[135] and hydrosilylation[136] of vinyl boronic esters have all been reported and give access to enantioenriched organoboronic esters primed for further transformations.



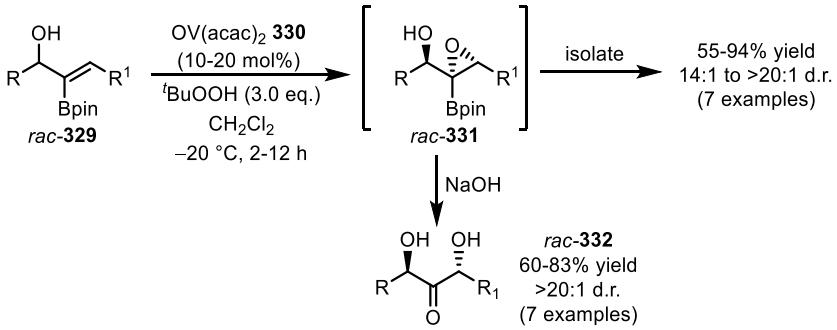
Scheme 66. Hydrofunctionalisation of vinyl boronic esters (polymethylhydroxysilane (PMHS))

Vinyl boronic esters, such as **313**, can also be converted into the corresponding ketones **326** through oxidation with basic hydrogen peroxide (Scheme 67).[137-138] The mechanism involves nucleophilic attack of peroxide to give boronate complex **327**, which undergoes 1,2-migration with loss of hydroxide to give borate **328**. This intermediate undergoes hydrolysis and tautomerization to deliver ketone **326**.



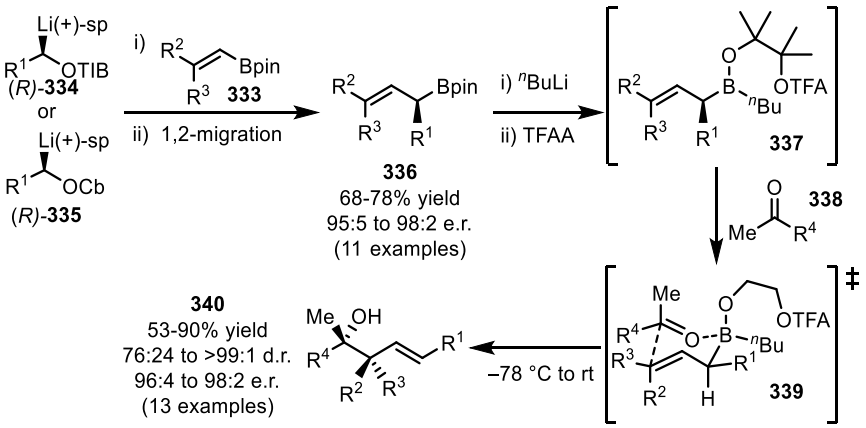
Scheme 67. Oxidation of vinyl boronic esters

Walsh and co-workers reported the synthesis of epoxy boronic esters *rac*-**331** from vinyl boronic esters *rac*-**329**, which was achieved using *tert*-butyl hydroperoxide in the presence of vanadium catalyst **330** (Scheme 68).[139] It was found that the epoxy boronic esters could be converted into 2-keto-1,2-*anti*-diols *rac*-**332** upon treatment with sodium hydroxide. Using a one-pot procedure, the diol products were obtained in 60-83% yield and with excellent diastereoselectivity.



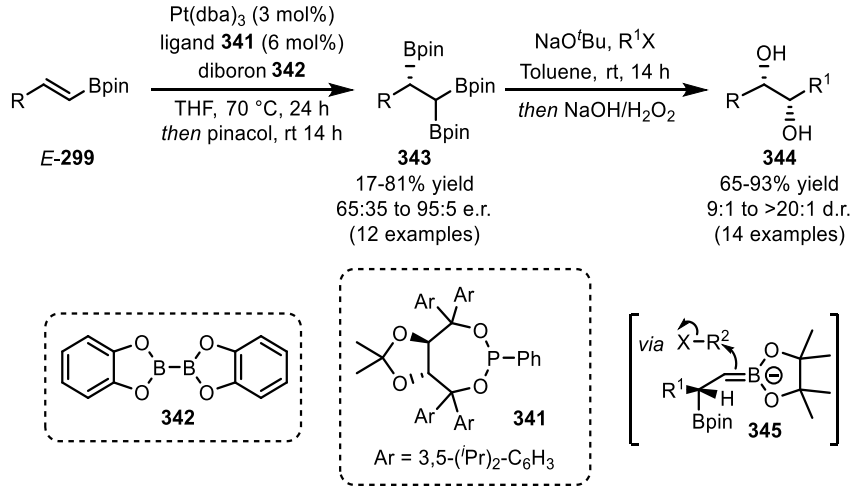
Scheme 68. Epoxidation of vinyl boronic esters (acetylacetonato (acac))

Vinyl boronic esters have also been shown to undergo homologation, a particularly useful transformation that provides access to allylic boronic esters, which are important intermediates in their own right (Scheme 69).[137][140] Reaction of vinyl boronic esters **333** with lithiated TIB esters (*R*)-**334** or lithiated carbamates (*R*)-**335** gave the corresponding allylic boronic esters **336** in good yields and enantiopurities. Treatment of these products with ^{n}BuLi, followed by trifluoroacetic anhydride (TFAA), gave borinic ester intermediates **337**, which engaged in allylboration reactions with ketones **338** to deliver enantioenriched tertiary alcohols **340** bearing contiguous quaternary stereocentres.



Scheme 69. Lithiation–borylation–allylboration sequence

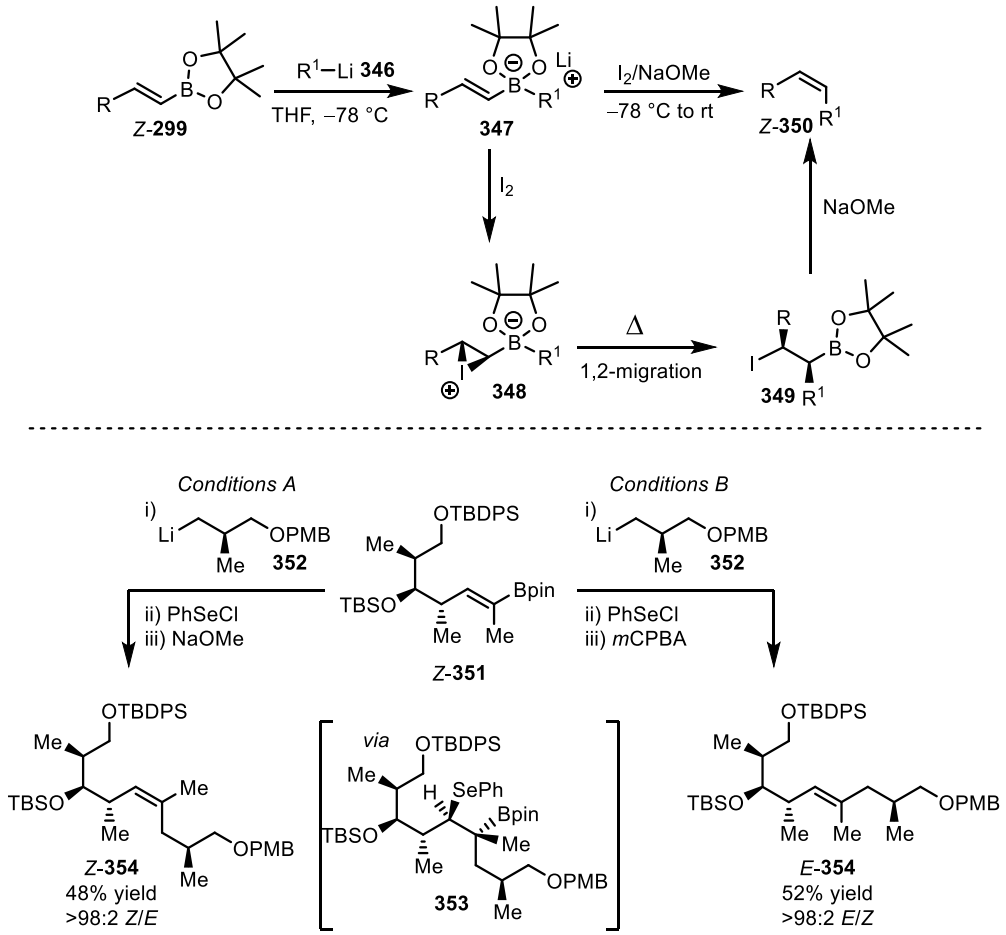
Morken and co-workers developed an enantioselective diboration reaction that converted vinyl boronic esters *E*-**299** into tris-boryl compounds **343** with good enantioselectivity (Scheme 70).[141] The products were found to undergo deborylative alkylation upon treatment with sodium *tert*-butoxide and an alkyl halide to give, after oxidation, the corresponding diols **344** in 65-93% yield and with excellent diastereoselectivity. The stereoselectivity was attributed to the reaction proceeding *via* intermediate **345**, which was anticipated to be the most nucleophilic conformer owing to hyperconjugation from the C–B σ-bond into the C–B π-bond**.**



Scheme 70. Enantioselective diboration of vinyl boronic esters *E*-**299** and deborylative alkylation of tris-boronic esters **343**

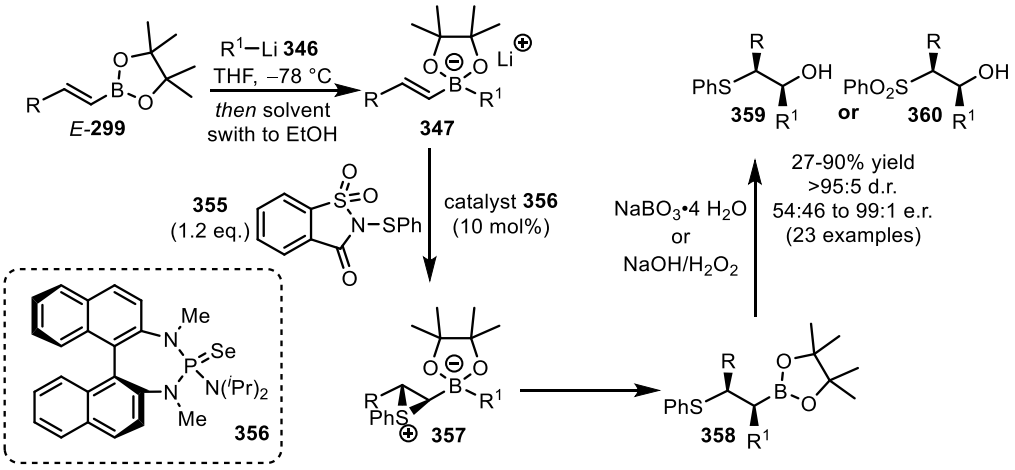
One of the most useful applications of vinyl boronic esters in organic synthesis is the Zweifel coupling reaction (Scheme 71).[142-143] Treatment of vinyl boronic ester *E*-**299** with an organolithium reagent **346** leads to vinylboronate **347**. Reaction of iodine with

347 results in iodonium **348**, which, upon warming, undergoes 1,2-migration to give **349** (in some cases ring-opening of iodonium **348** may occur at cryogenic temperatures). Finally, addition of sodium methoxide triggers an *anti*-elimination of β-iodo boronic ester **349** to give alkene *Z*-**350**. The reaction is stereospecific and therefore the geometry of the alkene product is dependent on that of the starting vinyl boronic ester. Aggarwal and co-workers found that iodine could be replaced with phenylselenium chloride (Conditions A) to give a reaction that proceeds by an analogous mechanism to the procedure of Zweifel, but *via* a selenium intermediate rather than an iodonium species.[144] In addition, they found that the intermediate β-selenyl boronic ester, such as **353**, could be oxidised with *m*CPBA to give a selenoxide species (Conditions B), which subsequently underwent a *syn*-elimination to provide the corresponding *E*-alkene products. Notably, these two methods allow stereodivergent access to both alkene isomers from the same vinyl boronic ester precursor, which was impressively demonstrated in the synthesis of *E*- and *Z*-**354**.



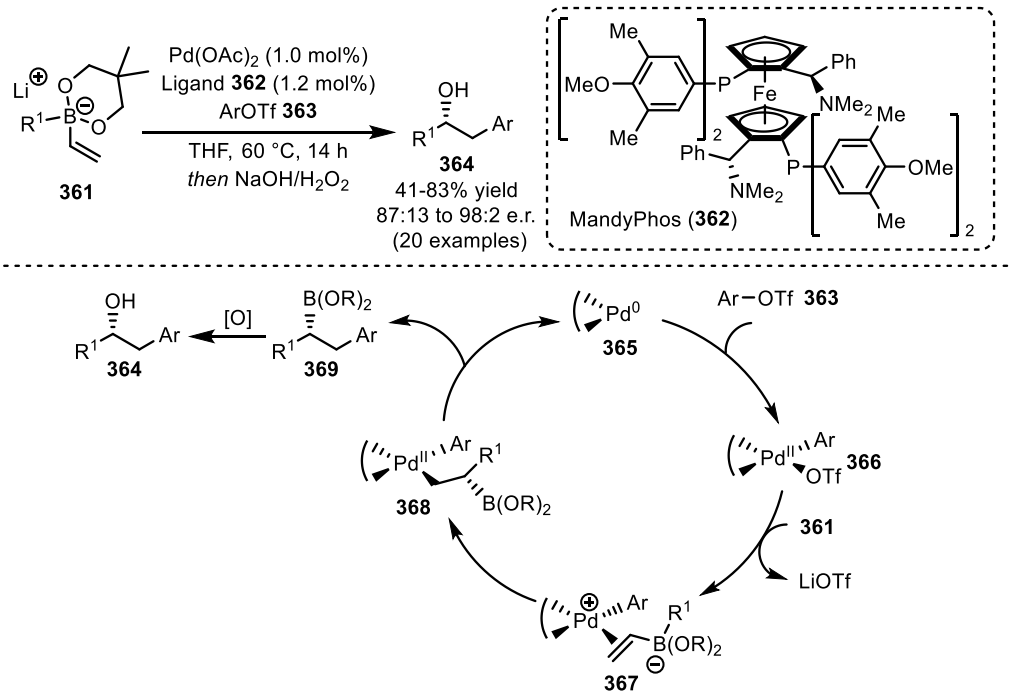
Scheme 71. Zweifel olefination and Aggarwal's stereodivergent Zweifel reaction

The Zweifel coupling reaction was recently adapted by Denmark and co-workers to gain access to chiral non-racemic β-sulfenyl boronic esters **358** (Scheme 72).[145] Treatment of vinylboronates **347** with sulfenylating agent **355** in the presence of chiral Lewis base **356** lead to enantioenriched thiranium intermediates **357**, which after 1,2-migration and oxidation gave alcohol products **359** or **360** in moderate to excellent yields and with high enantioselectivity.



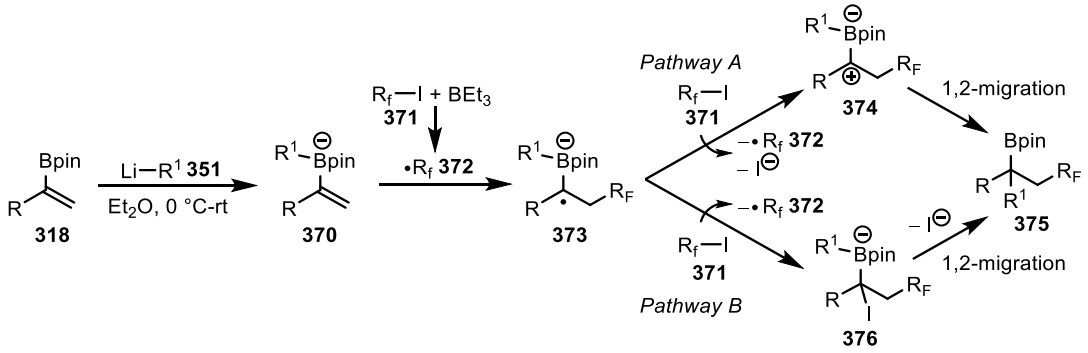
Scheme 72. Enantioselective sulfenylation of vinyl boronates

Morken and co-workers have shown that 1,2-migration of vinyl boronates can be triggered by the presence of a cationic Pd catalyst in a process termed conjunctive cross-coupling (Scheme 73).[146] By using MandyPhos (**362**) as the chiral ligand, the reaction gave access to enantioenriched neopentyl boronic esters **369**, which, after oxidation, gave the corresponding alcohol products **364**. The catalytic cycle commences with oxidative addition of the Pd^0 catalyst **365** into the C–OTf bond of aryl triflate **363**. After ligand dissociation, cationic palladium species **367** induces a 1,2-migration with concurrent trapping at palladium to give intermediate **368**, which is the stereodetermining step of the reaction. Finally, reductive elimination regenerates Pd^0 catalyst **365** and delivers neopentyl boronic ester **369**, which is subsequently oxidised to give alcohol **364**.



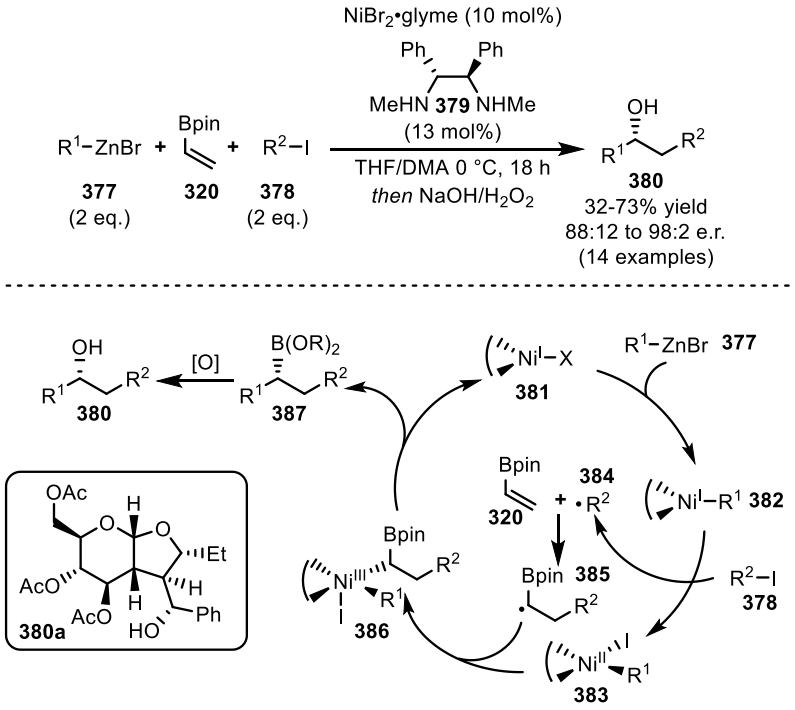
Scheme 73. Morken's conjunctive cross-coupling reaction

In separate reports, the groups of both Studer and Aggarwal demonstrated that vinyl boronates could react with alkyl radicals to deliver tertiary boronic ester products.[147-148] In Studer's process, triethyl borane was added as a radical initiator to convert the perfluoroalkyl iodide **371** into the corresponding alkyl radical **372**, which subsequently added to the terminal position of the vinylboronate **370** to give an α-boryl radical anion **373** (Scheme 74). Two pathways (A and B) were then possible, the first involved an electron transfer process with another molecule of **371** to give zwitterionic intermediate **374**, which undergoes a spontaneous 1,2-migration to deliver boronic ester **375** (Pathway A). The second pathway involves iodine abstraction of **371** by radical intermediate **373** to give α-iodo boronate **376**, which can then undergo a Matteson-type 1,2-migration to deliver product **375** (Pathway B). Aggarwal's procedure differed from Studer's in that visible light was used to generate the radical species, *via* homolysis of the C-I bond. Using these milder conditions, the authors were able to incorporate a wider range of alkyl iodides and boronic esters into the reaction.



Scheme 74. Studer's radical alkylation of vinyl boronate complexes

Morken and co-workers have recently developed an enantioselective process for the alkylation of vinyl boronates.[149] The reaction of chiral non-racemic nickel complex **381**, vinyl boronic ester **320**, organozinc reagents **377** and alkyl iodides **378** gave, after oxidation, a variety of enantioenriched alcohol products **380** with excellent stereocontrol (Scheme 75). The advantage of using organozinc reagents rather than organolithium reagents is the increased functional group tolerance, which was demonstrated by preparation of sugar derivative **380a**. The proposed mechanism begins with transmetallation of organozinc **377** and nickel catalyst **381** to give Ni^{I} species **382**, which is oxidised by alkyl iodide **378** to give **383**, with release of carbon centred radical **384**. Radical **384** reacts with vinyl boronic ester **320** to form α-boryl radical **385**, which reacts with Ni^{II} species **383** to give **386**. Reductive elimination of **386** gives enantioenriched organoboronic ester **387**, which after oxidation delivers alcohol **380**.

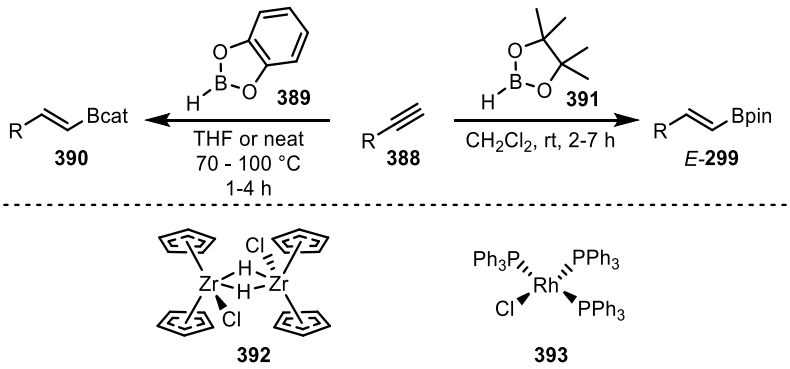


Scheme 75. Morken's enantioselective radical polar cross-over reaction

(dimethylacetamide (DMA))

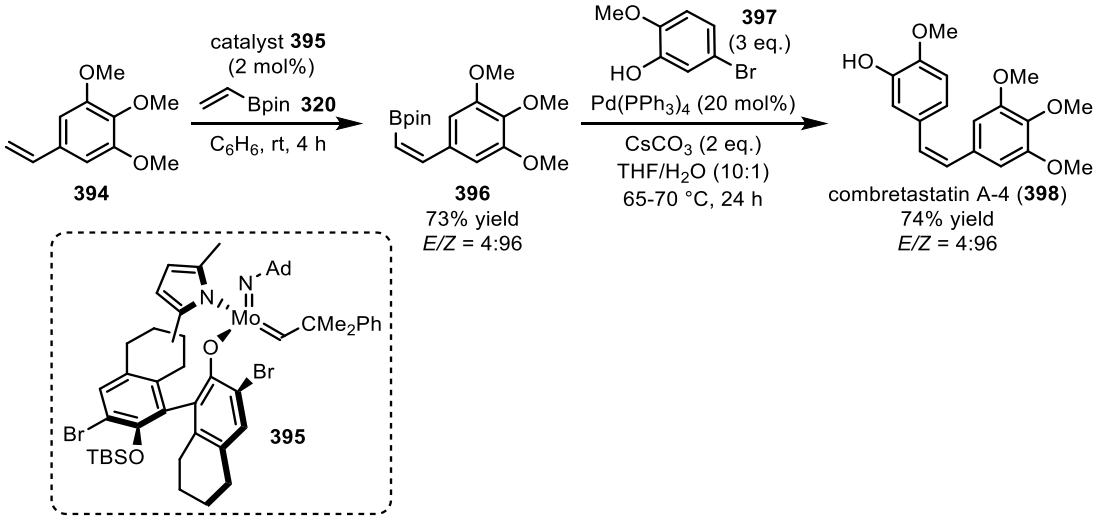
5.1.2. *Methods for the Preparation of Vinyl Boronic Esters*

Due to the synthetic value of vinyl boronic esters, there have been many methods developed for their preparation. Perhaps the most extensively utilised of these procedures is the hydroboration of alkynes. First reported by Brown *et al*.,[150] treatment of terminal alkyne **388** with catechol borane (HBcat) (**389**) gave *anti*-Markovnikov product **390** in good yield and as a single isomer (Scheme 76). Knochel and co-workers modified this protocol to employ pinacol borane (HBpin) (**391**) as the hydroboration reagent, with the added value being that pinacol boronic esters are generally more stable than catechol boronic esters, particularly towards column chromatography.[151] Modern variations of this reaction typically employ a catalyst, such as the Schwartz reagent **392** or Wilkinson catalyst **393**.[152-153]



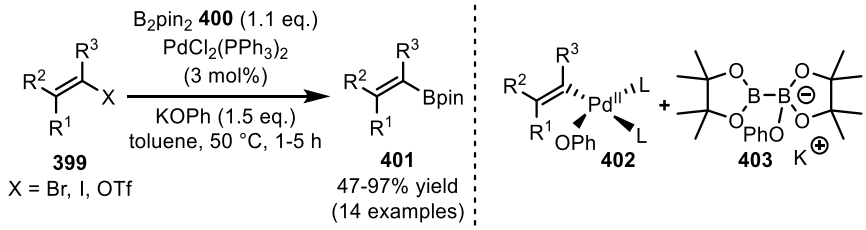
Scheme 76. Hydroboration of alkynes for the preparation of vinyl boronic esters

Cross-metathesis is a very useful method for the stereoselective preparation of *Z*-vinyl boronic esters (Scheme 77).[154] Hoveyda and co-workers reported the reaction of monosubstituted alkenes and vinyl boronic ester **320** in the presence of molybdenum catalyst **395**, which gave the corresponding *Z*-vinyl boronic ester products in high yields and with excellent stereoselectivity. To demonstrate the synthetic utility, the methodology was used to prepare anti-cancer agent **398** in two steps from styrene **394**.



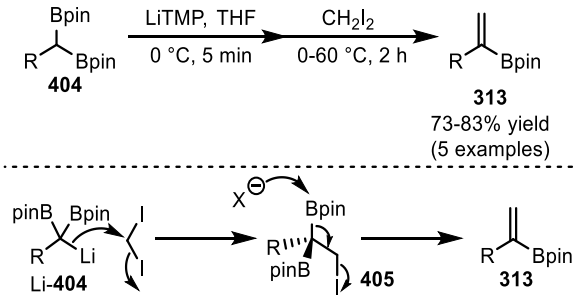
Scheme 77. Cross-metathesis for the preparation of *Z*-vinyl boronic esters

In 2002, Miyaura *et al.* reported that vinyl boronic esters **401** could be prepared by the palladium-catalysed borylation of vinyl halides and triflates **399** (Scheme 78).[155] The reaction is stereospecific and proceeds with retention of stereochemistry with respect to the parent alkene, making it a useful method for the preparation of stereodefined vinyl boronic esters. The catalytic cycle is analogous to that of the Suzuki-Miyaura coupling (see Scheme 64, page 70), however differs in that the transmetallation event occurs between vinyl palladium species **402** and boronate **403**.



Scheme 78. Miyaura borylation reaction

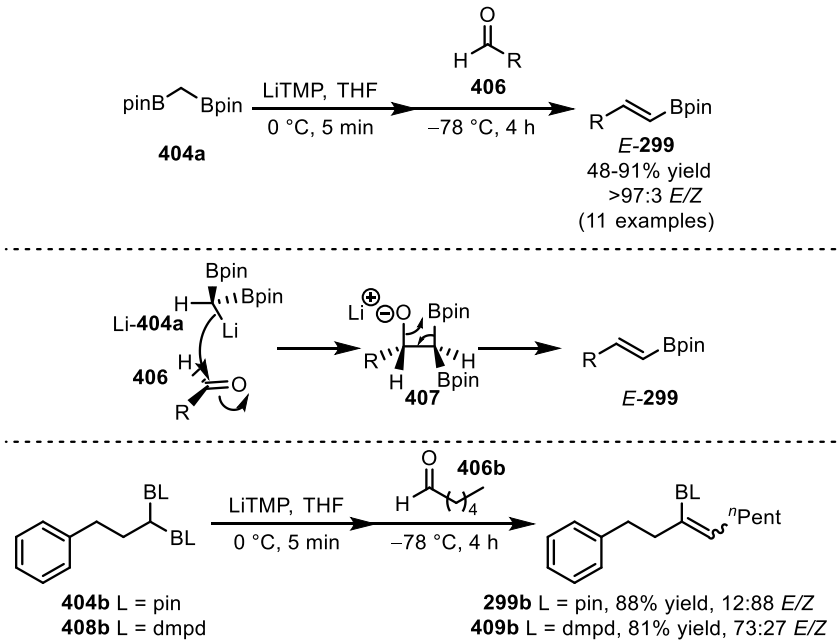
Morken and co-workers demonstrated that 1,1-disubstituted vinyl boronic esters **313** could be prepared by the reaction of lithiated diborons Li-**404** with diiodomethane (Scheme 79).[156] Lithiation of the diboron compounds **404** was achieved with LiTMP in THF at 0 °C and subsequent addition of diiodomethane gave the corresponding products **313** in moderate to excellent yields. Presumably, the reaction proceeds by nucleophilic attack of diiodomethane by Li-**404**, followed by *anti*-elimination of **405** to give vinyl boronic ester products **313**.



Scheme 79. Reaction of lithiated diborons and diiodomethane

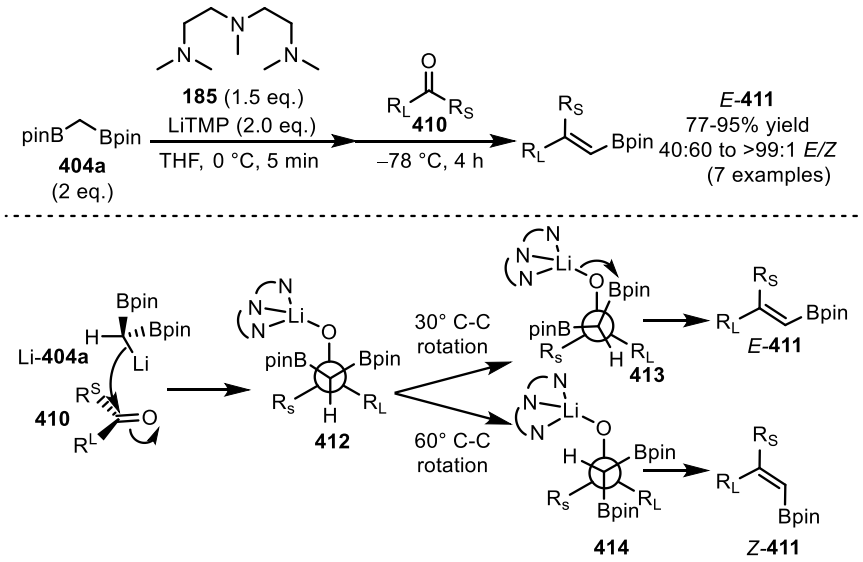
In the same report, Morken *et al.* demonstrated that vinyl boronic esters could also be obtained by the reaction of lithiated diboron **404a** with aldehydes **406** (Scheme 80). Reaction of **404a** with aliphatic and aromatic aldehydes gave the corresponding *E*-vinyl boronic ester products *E*-**299** in good yield and with high stereoselectivity. The reaction proceeds by addition of lithiated species **404a** into aldehyde **406** to give **407**. The authors proposed nucleophilic attack occurs in accordance with the observations of Taylor *et al.*, with the H-substituent of Li-**404a** being located between the substituents of the carbonyl.[157] Intermediate **407** subsequently undergoes a boron-Wittig reaction to deliver vinyl boronic ester *E*-**299**. When this protocol was extended to a substituted bis-pinacol diboron, such as **404b**, the *Z*-product (*Z*-**299b**) was obtained selectively. The authors found that, by changing the ligand on boron to 1,3-dimethylpentane-1,3-diol (dmpd)(**408b**), selectivity for the *E*-product (**409b**) could be restored. The authors utilised

these diverging pathways to prepare a variety of *E*- and *Z*-vinyl boronic ester products in excellent yield and, in some cases, with high stereoselectivity.



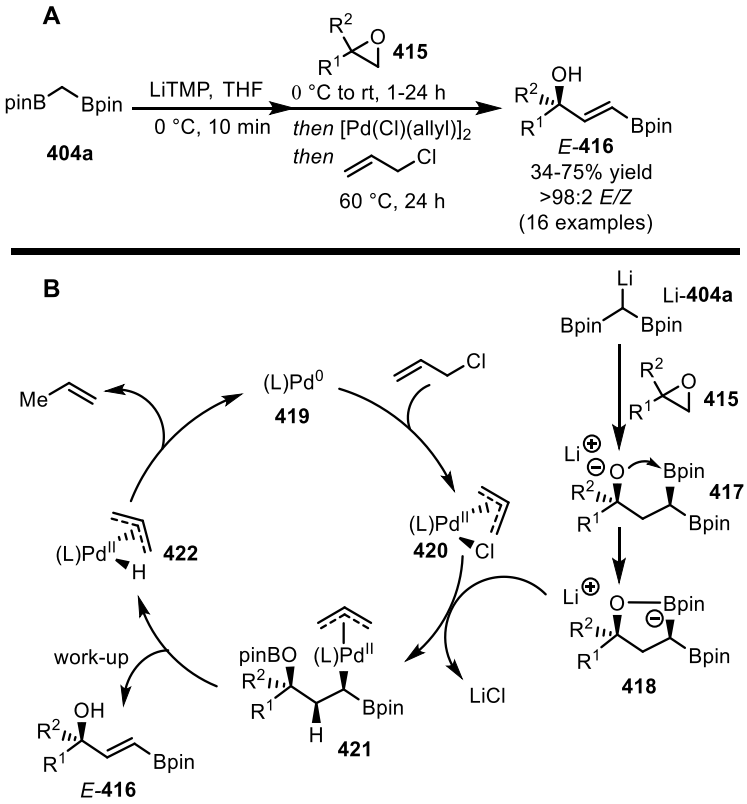
Scheme 80. Preparation of vinyl boronic esters from the reaction of lithiated diboron compounds and aldehydes

More recently, Morken and co-workers expanded the scope of this reaction to include ketones **410** (Scheme 81).[158] The procedure is analogous to that shown above (Scheme 80) but employs triamine **185** as an additive, which was found be crucial for obtaining the *E*-trisubstituted vinyl boron products (*E*-**411**) in a stereocontrolled fashion. Triamine **185** is proposed to break up alkoxide aggregates that would otherwise hinder the boron-Wittig process.[159] The authors proposed that in general the elimination process *via* **413** must be faster than bond rotation, as the *E*-products (*E*-**411**) were formed selectively. Where elimination is slow, bond rotation places the H-substituent proximal to the large alkoxy group, as in **414**, which would lead to the *Z*-product (*Z*-**411**).



Scheme 81. Preparation of vinyl boronic esters from the reaction of Li-**404a** and ketones

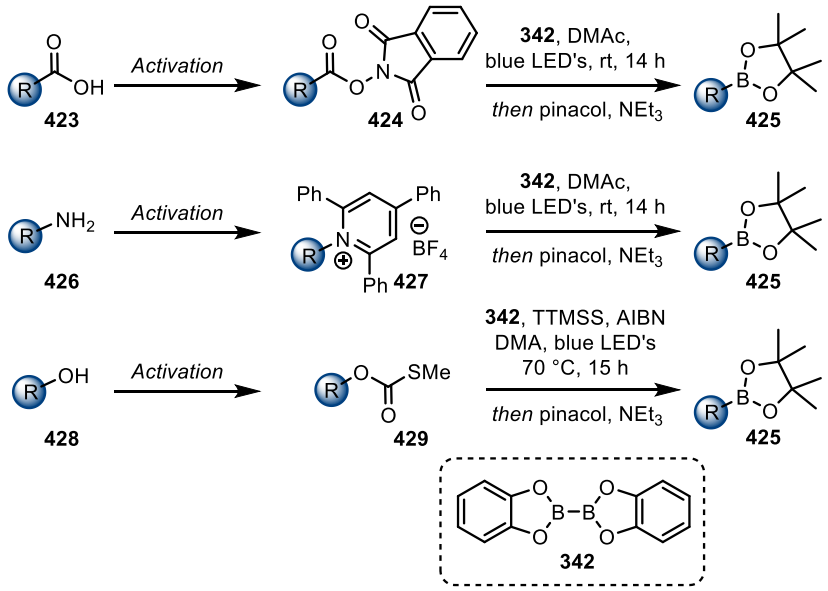
Meek and co-workers reported that treatment of epoxides **415** with lithiated diboron **404a** and a palladium catalyst could be used to access vinyl boronic esters *E*-**416** with excellent stereoselectivity (Scheme 82).[160] The reaction was compatible with mono- and 1,1-disubstituted epoxides, however trisubstituted epoxides gave only traces of product. When an enantioenriched epoxide was used, the product was obtained with complete stereospecificity, making this a useful procedure for the preparation of chiral non-racemic vinyl boronic esters. The mechanism begins by addition of Li-**404a** into the terminal position of epoxide **415**. The oxyanion of **417** co-ordinates to one of the boron atoms to form boronate **418**, which is primed to undergo transmetallation with Pd^{II} species **420**, which itself is generated upon oxidative addition of catalyst **419** into allyl chloride. β-Hydride elimination of **421** followed by hydrolysis upon work-up delivers *E*-**414**.



Scheme 82. Preparation of vinyl boronic esters from the reaction of Li-**404a** and epoxides under palladium catalysis

5.2. Project Outline

While many methods for the preparation of vinyl boronic esters have been reported, at the outset of this project there was no practical procedure for the homologation of boronic esters into vinyl boronic esters. This strategy was attractive to us, as recent efforts by the scientific community have enabled the conversion of feedstock materials such as carboxylic acids,[161] amines,[162] and alcohols[163] into organoboronic esters (Scheme 83). As a result of these developments, a vast range of sp^3-rich organoboronic esters are readily accessible and we hoped that, through development of a vinylidene homologation protocol, we might use these compounds to access novel vinyl boronic esters. This idea was particularly appealing when considering that pharmaceutical companies, who frequently employ vinyl boronic ester intermediates in their drug discovery and process programmes,[127] are under increasing pressure to "escape flatland" and further explore chemical space.[164]

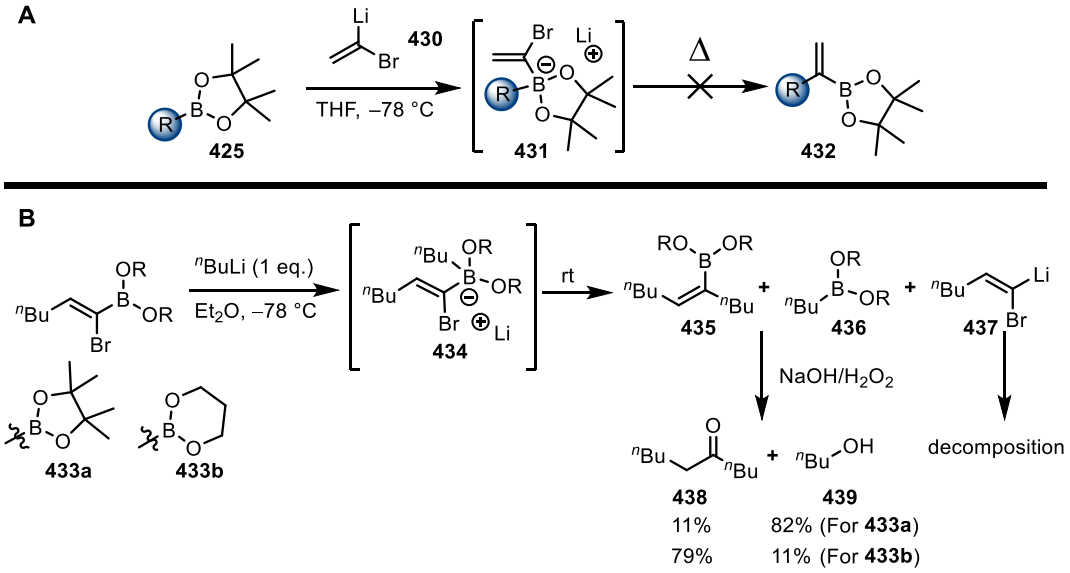


Scheme 83. Borylation of feedstock materials

(azobisisobutyronitrile (AIBN), tris(trimethylsilyl)silane (TTMSS))

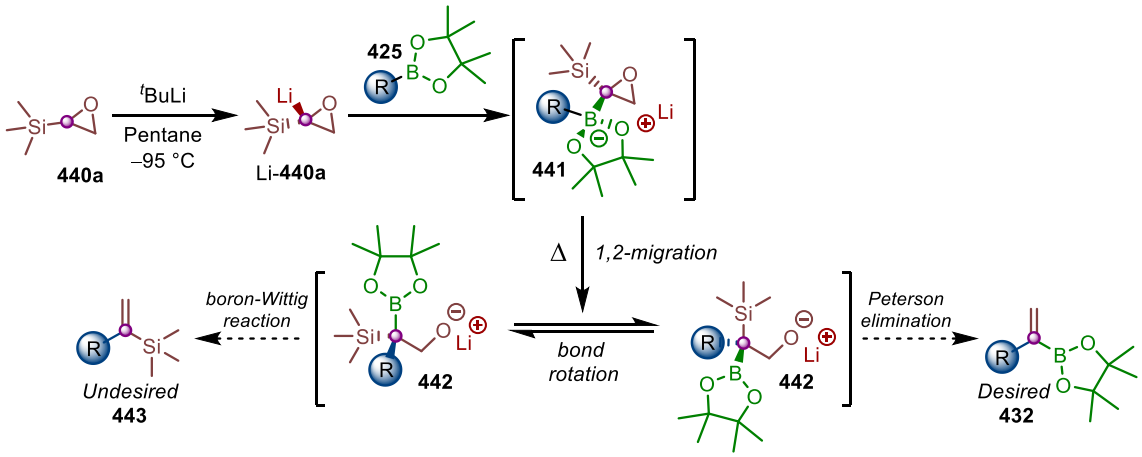
Perhaps the most obvious method to achieve the vinylidene homologation of a boronic ester is through treatment with an α-halovinyl lithium reagent, such as **430** (Scheme 84A). However, Brown and co-workers demonstrated that this approach is not viable, as treatment of α-bromovinyl boronic ester **443a** with ^{n}BuLi at low temperature, followed by warming of the reaction mixture and oxidation delivered desired product **438** in just

11% yield by gas chromatography (GC) (Scheme 84B).[165] ^{n}Butanol (**439**) was obtained as the major product, which meant that boronate complex **431** must preferentially decompose to boronic ester **436** and α-bromovinyl lithium species **437** at elevated temperatures, rather than undergo the desired 1,2-migration process. The authors demonstrated that the yield of ketone **438** could be improved by using 1,3-propane diol as the ligand on boron. In this case, substrate **433b**, after oxidation of the intermediate vinyl boronic ester **435**, ketone **438** was observed in 79% GC yield. Despite this enhanced yield, the utility of this reaction is restricted by the limited availability and stability of propanediol boronic esters, especially when compared to pinacol boronic esters.



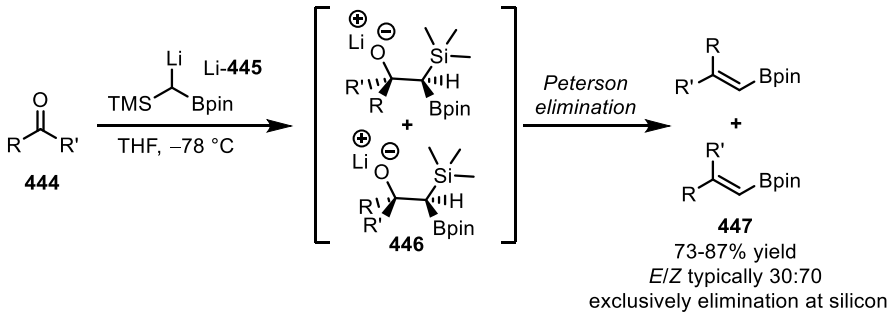
Scheme 84. A) Homologation of pinacol boronic ester **425** with lithiated species **430** B) Reaction of α-bromoboronic esters **433a** and **433b** with ^{n}BuLi

During our work with lithiated epoxides (Chapter 4), it occurred to us to consider the outcome for a reaction between lithiated epoxysilane Li-**440a**[97] and boronic ester **425** (Scheme 85). We envisaged that, upon formation of boronate complex **441**, warming of the reaction mixture would instigate a 1,2-migration to give α-silyl-β-alkoxyboronate **442**. From this intermediate two pathways were plausible; a Peterson elimination[166] to give vinyl boronic ester **432** or a boron-Wittig reaction to give vinyl silane **433**.



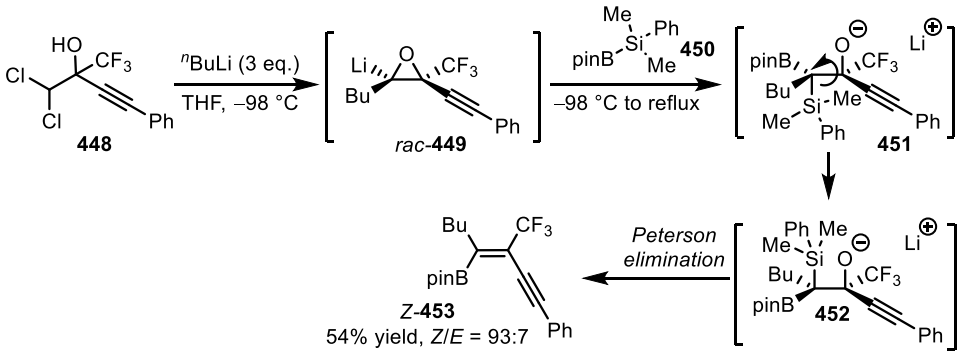
Scheme 85. Reaction proposal

A report from Matteson and co-workers suggested that the Peterson elimination might be favoured over the boron-Wittig reaction (Scheme 86).[167] They found that reaction of a range of ketones **444** with lithiated species Li-**445** at low temperature, followed by warming, gave exclusively the vinyl boronic esters *E*- and *Z*-**447**, the products of elimination at silicon. Unfortunately, this chemoselectivity was not rationalised by the authors.



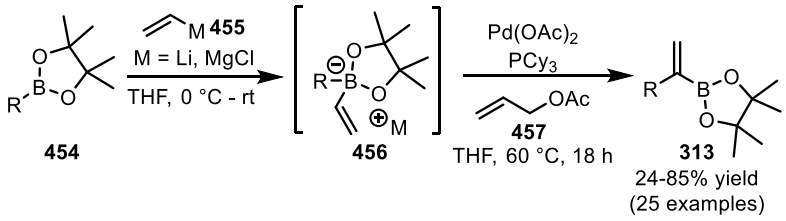
Scheme 86. Matteson's precedent for a Peterson elimination being favoured over a boron-Wittig reaction

Hiyama *et al.* provided further precedent for selective elimination at silicon over boron (Scheme 87).[168] Reaction of boronic ester **450** with lithiated species *rac*-**449**, which was generated *in-situ* from chlorohydrin **448**, delivered vinyl boronic ester *Z*-**453** in 54% yield as the sole product. Presumably, boronate complex **451** underwent 1,2-migration to deliver β-alkoxyboronic ester **452**, which after elimination at silicon gave *Z*-**453**.



Scheme 87. Hiyama's precedent for a Peterson elimination being favoured over a boron-Wittig reaction

During the conduction of our investigation, Morken and co-workers reported their own method for the vinylidene homologation of boronic esters (Scheme 88).[169] The reaction gave access to a range of 1,1-disubstituted vinyl boronic esters **313** in moderate to high yields.



Scheme 88. Morken's vinylidene homologation

Whilst this protocol is undoubtedly useful, it did have several disadvantages when compared to our proposal. Firstly, the method required a transition-metal catalyst, which makes it somewhat expensive and unsustainable, as well as access to a glovebox, which rendered the transformation inaccessible for many synthetic chemists. Therefore, we continued our investigation with the hope that our vinylidene homologation might serve as a transition-metal- and glovebox-free alternative to that of Morken.

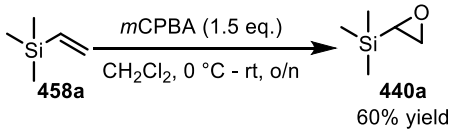
5.3. Results & Discussion

5.3.1. *Notes on Collaboration*

The data presented in this section has been published in part in the following communication: Fordham, J. M.; Grayson, M. N.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2019**, *58*, 15268–15272. Some boronic ester starting materials, denoted with an (ǂ), were prepared by other members of our lab as part of the Aggarwal boronic ester database. Computational experiments were performed by Dr. Matt Grayson, Prof. Craig Butts and Oliver Dutton, denoted with an (*), and are included in this thesis to provide a complete picture of the work.

5.3.2. *Vinylidene Homologation of Boronic Esters*

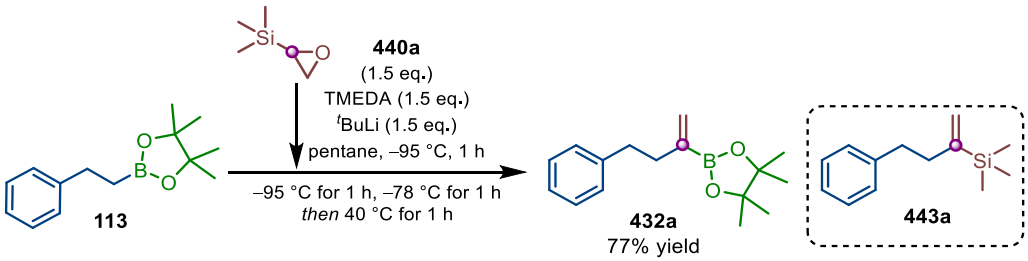
Encouraged by the reports of Matteson and Hiyama, we prepared epoxysilane **440a** by treating vinyl silane **458a** with *m*CPBA (Scheme 89). While the reaction proceeded smoothly, isolation of the volatile epoxysilane product (boiling point (B.P.) = 110 °C) by fractional distillation proved challenging, due to its tendency to azeotrope with the reaction solvent. Nevertheless, after a careful distillation **440a** was isolated in 60% yield and free of CH_2Cl_2, which was crucial for the subsequent lithiation–borylation step.



Scheme 89. Synthesis of epoxysilane **440a**

We then attempted the vinylidene homologation reaction (Scheme 90). Phenethyl boronic ester **113** was added to an excess of lithiated epoxysilane Li-**440a**, which was generated according to Eisch's procedure.[97] After stirring for 1 h at –95 °C, the reaction was warmed to –78 °C to further facilitate boronate complex formation. After stirring for 1 h at –78 °C, the reaction was warmed to ambient temperature and subsequently stirred for 1 h at 40 °C to effect both 1,2-migration and elimination. At this point, ^{11}B NMR analysis indicated that 1,2-migration was almost complete (small peak at 7 ppm) and a new peak at 30.2 ppm was observed, which was indicative of formation of a vinyl boronic ester

species (Figure 7). The peak corresponding to boronate complex persisted even with extended reaction times. Importantly, there was no evidence of borate (~20 ppm), which suggested that the boron-Wittig reaction, which leads to vinyl silane **443a**, was not operative. After work-up and chromatographic purification, vinylidene homologation product **432a** was isolated in a gratifying 77% yield. Starting boronic ester **113** was recovered in 10% yield and there was no evidence of vinyl silane product **443a**. It is worth noting the significance of the additional 1 h at –78 °C, as warming directly from –95 °C to 40 °C gave **432a** in just 50% yield.



Scheme 90. Initial hit for the vinylidene homologation reaction

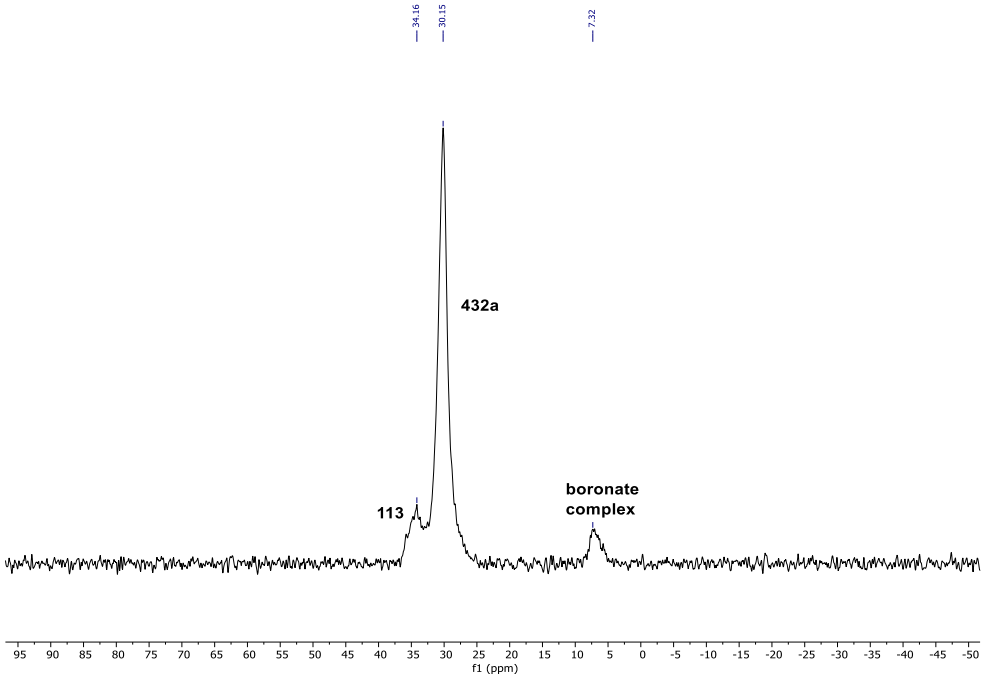
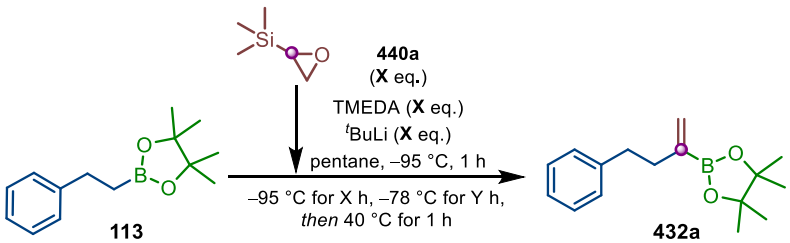


Figure 7. ^{11}B NMR spectrum for the reaction displayed in Scheme 90

In an attempt to improve conversion of starting boronic ester **113** to product **432a**, the equivalents of lithiated species Li-**440a** were increased, however no enhancement in yield was observed (Table 27, Entry 2). Next, we considered whether lithiation was reaching completion. If not, we would have an excess of ^{t}BuLi that might react with boronic ester **113** and lead to a persistent boronate complex, which would account for the 10% of mass

balance that was lost (Entry 1). To address this possibility, the amount of epoxysilane **440a** was increased relative to TMEDA **27** and ^{t}BuLi (Entry 3), however this did not have the desired impact, and curiously only a trace amount of starting boronic ester **113** was observed. Upon lithiation of epoxysilane **440a**, the reaction mixture exists as a white suspension, which led us to wonder whether insoluble aggregates might be hindering the reaction success. Thus, the lithiation was performed at a lower concentration (Entry 4), which did result in a more homogeneous reaction mixture, but did not influence the reaction outcome. Unsurprisingly, increasing the concentration of the reaction (Entry 5) did not improve the yield of **432a** and generally resulted in a less reproducible procedure. To probe the stability of lithiated species Li-**440a**, the reaction was immediately warmed to –78 °C following boronic ester addition and subsequently stirred for 2 h (Entry 6). Under these conditions, vinyl boronic ester product **432a** and starting boronic ester **113** were observed in 51% and 40% yield respectively, which indicated that lithiated species Li-**440a** is chemically unstable at this temperature.

Table 27. Optimisation table for the vinylidene homologation



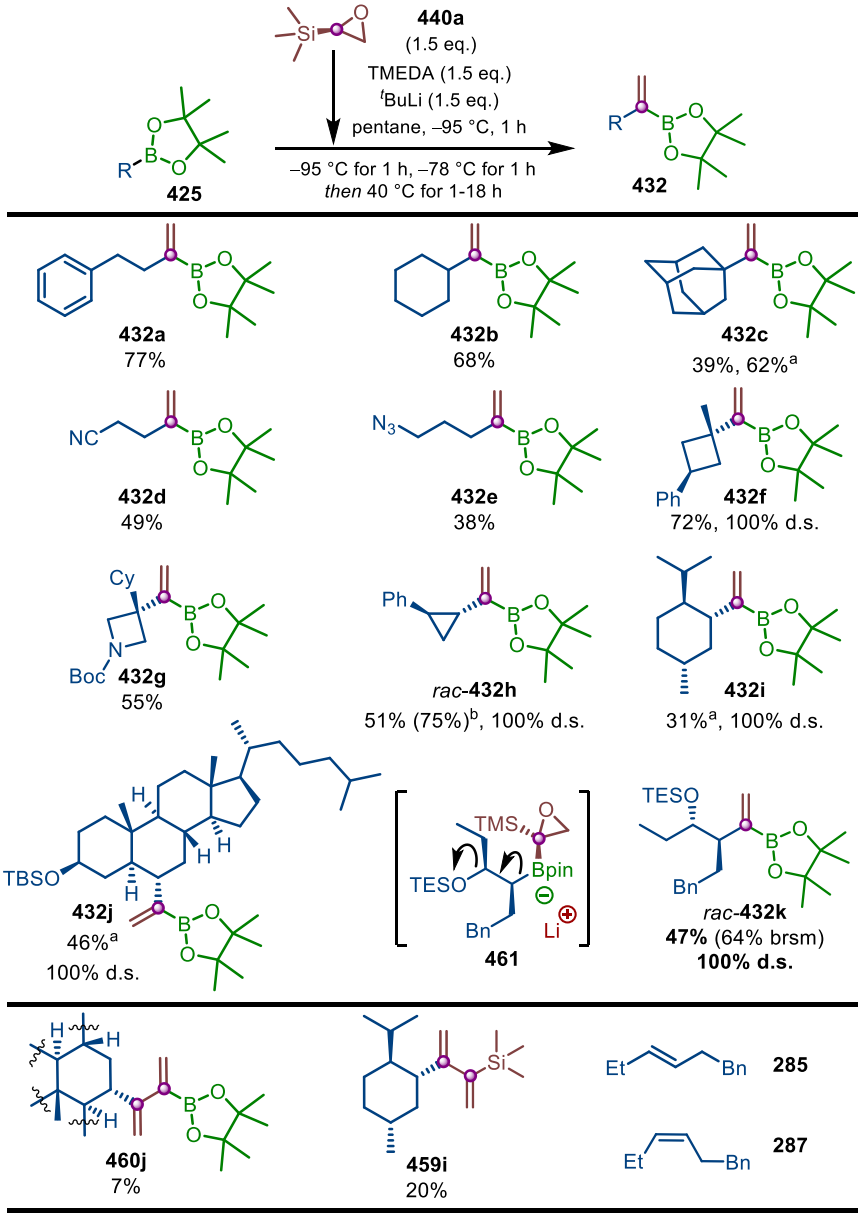
Entry	Epoxide (eq.)	TMEDA (eq.)	^{t}BuLi (eq.)	Concentration (M)	X/Y (h)	Yield[a]	Comments
1	**1.5**	**1.5**	**1.5**	**0.15**	**1/1**	**N.D. (77%)**	**10% 113 remains**
2	2.0	2.0	2.0	0.15	1/1	76%	Trace **113** remains
3	2.0	1.5	1.5	0.15	1/1	76%	Trace **113** remains
4	1.5	1.5	1.5	0.10	1/1	76%	15% **113** remains
5	1.5	1.5	1.5	0.25	1/1	75%	15% **113** remains
6	1.5	1.5	1.5	0.15	0.05/2	51%	40% **113** remains

[a] Corresponds to NMR yield using 1,3,5-trimethoxybenzene as internal standard, isolated yields are reported in parentheses.

With optimal reaction conditions in hand (Table 27, Entry 1), we investigated the scope of the reaction (Table 28). The reaction time at 40 °C for each substrate was adjudged by ^{11}B NMR analysis of the reaction mixture, with disappearance of the peak for boronate complex (~7 ppm) indicating reaction completion. The reaction was found to be compatible with more sterically hindered secondary and tertiary boronic esters, as

products **432b** and **432c** were isolated in yields of 68% and 39% yield respectively. It was found that, by increasing the equivalents of lithiated species Li-**440a**, the yield of **432c** could be increased to 62%. Base and nucleophile sensitive groups were found to be tolerated as vinyl boronic esters **432d** and **432e**, containing cyano and azidyl substituents, were obtained in 49% and 38% yield respectively. The corresponding starting boronic esters **425d** and **425e** were observed in the crude reaction mixtures but were not recovered. Next, we were keen to prepare pharmaceutically relevant vinyl boronic esters and thus cyclobutyl and azetidinyl substrates **432f** and **432g** were investigated. The corresponding vinyl boronic esters **432f** and **432g** were isolated in 72% and 55% yield respectively, with the former being obtained with complete diastereospecificity. Cyclopropyl vinyl boronic ester *rac*-**432h** was observed in an NMR yield of 75% but could only be isolated in 51% yield, due to a tendency to decompose during chromatography, even after deactivation of the silica gel with triethylamine. The methodology was found to be compatible with more complex substrates. Menthyl- and cholesteryl-derived vinyl boronic esters **432i** and **432j** were obtained in yields of 31% and 46% and as single diastereomers. Interestingly, over-homologation products **459i** and **460j** were obtained in 20% and 7% yield respectively, which was very surprising considering that lithiated species Li-**440a** had demonstrated limited stability even at –78 °C (Table 27, Entry 6). Finally, polyketide-type substrate *rac*-**282** was subjected to the reaction conditions and gave vinyl boronic ester **432k** in 47% yield (64% brsm). Alkene **285**, which arises from desilylation of starting boronic ester *rac*-**282**, followed by elimination (see page 65), was observed in 11% NMR yield. Significantly, no β-elimination **461** had occurred as alkene **287** was not observed in the reaction mixture.

Table 28. Scope of vinylidene homologation for aliphatic boronic esters

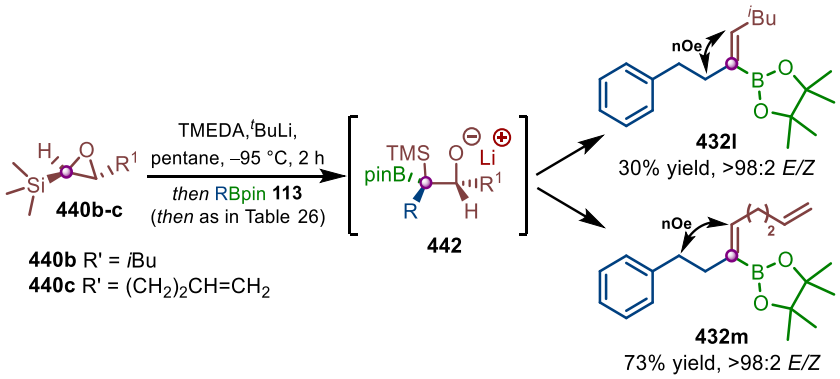


Yields are of isolated products. Diastereomeric ratios were determined by ^{1}H NMR analysis of the isolated products. [a]Reaction performed using 2.5-3.0 eq. of lithiated epoxide. [b]Yield in parentheses was determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

As lithiated epoxysilanes are configurationally stable at low temperature,[97] it was expected that a diastereopure *trans*-substituted epoxysilane would deliver the corresponding (*E*)-vinyl boronic ester as a single isomer (Scheme 91). Epoxysilanes **440b** and **440c**, which were prepared from epoxides **462** and **463** using Hodgson's procedure (page 50),[109] were lithiated with stoichiometric ^{t}BuLi and TMEDA in pentane at –95 °C for 2 h. Addition of boronic ester **113** to the lithiated species, followed by heating, gave vinyl boronic esters **432l** and **432m** in 30% and 73% yield respectively and as single

ǂ Boronic esters **425c-j** were acquired from the Aggarwal boronic ester database

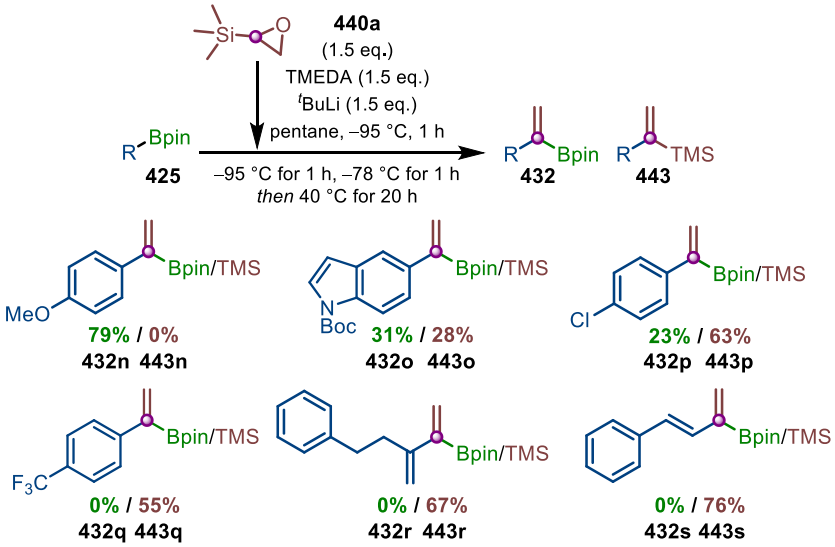
isomers. During the lithiation of epoxysilane **440b** a precipitate formed that inhibited stirring, which may have resulted in a diminished yield of **432l**. The stereochemistry of the double bond was confirmed for both substrates by use of the nuclear Overhauser effect (nOe), which was observed between the alkenyl proton and phenethyl group for both substrates, proof that the products possessed the expected *E*-geometry.



Scheme 91. Vinylidene homologation with substituted epoxysilanes **440b** and **440c**

Next, we applied the reaction conditions to a range of sp^2-hybridised boronic esters (Table 29). For these substrates, a longer reaction time was required owing to the poor migratory aptitude of aryl and vinyl substituents.[44] The reaction outcome was found to be highly dependent on electronics, while *p*-methoxyphenyl boronic ester **425n** gave the homologated product **432n** in 79% yield as the exclusive product, the less electron-rich indolyl boronic ester **425o** gave a mixture of vinyl boronic ester **432o** and vinyl silane **443o** in 31% and 28% yield respectively. For **425o**, styrene **464** was also observed and was found to be inseparable from vinyl silane **443o.** This side-product likely arises from protodeboronation and/or protodesilylation of **432o** and/or **443o**. The boron-Wittig pathway, that leads to the vinyl silane product, was even more prominent for more electron-deficient aryl boronic esters, as *p*-chlorophenyl boronic ester **425p** gave vinyl silane **443p** as the major product. The most extreme case was *p*-trifluoromethylphenyl boronic ester **425q**, which gave vinyl silane **443q** in 55% yield as the sole product. Furthermore, subjection of vinyl boronic esters **432a** and **425s** to the reaction conditions also resulted in the corresponding vinyl silane products **443r** and **443s** in 67% and 76% yield respectively.

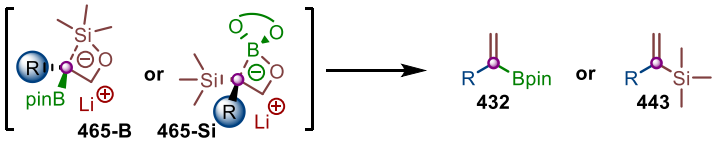
Table 29. Scope of vinylidene homologation for vinyl and aryl boronic esters[‡]



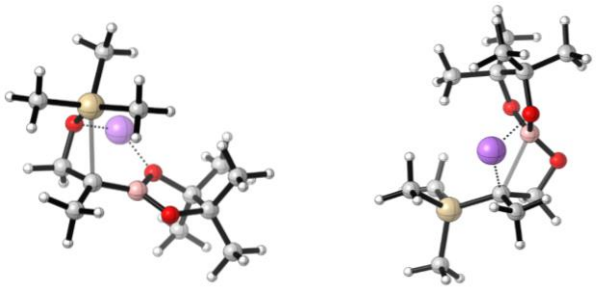
We were keen to investigate this divergence in mechanistic pathway using DFT*. The calculations were performed with Gaussian 16 at the B3LYP-D3(BJ)/6-311G(d,p)-IEFPCM(pentane)//B3LYP/6-31G(d) level of theory (Table 30). For both sp^2- and sp^3-hybridised boronic esters, the thermodynamic product was found to be the vinyl silane by over 3 kcal/mol. To understand the origins of product selectivity, the relative energies of the C–B and C–Si bond-breaking transition-states (TSs) were determined. Substrate **425t** (R = Me, Entry 1) was used as a model aliphatic boronic ester in order to reduce the number of conformations that had to be calculated. For this example, the C–Si bond breaking TS was favoured by 9.2 kcal/mol relative to the C–B bond breaking TS, displaying a strong preference for the vinyl boronic ester product (Figure 8). This is in good agreement with experimental results, as all aliphatic boronic esters gave the corresponding vinyl boronic ester products exclusively. For *p*-methoxyphenyl boronic ester **425n** (Entry 2) the C–Si bond breaking TS was favoured by 1.2 kcal/mol whereas, for indolyl boronic ester **425o** (Entry 3), the C–B bond breaking TS was favoured by 0.2 kcal/mol. These values are also in good agreement with experiment as **425n** gave vinyl boronic ester product **432n** exclusively, whilst **425o** gave both boronic ester **432o** and vinyl silane **443o** in similar quantities. Trifluoromethylphenyl boronic ester **425q** (Entry 4) and styrenyl boronic ester **425s** (Entry 5) favoured the C–B bond breaking TS by 1.4 kcal/mol and 5.6 kcal/mol respectively, which again was in good agreement with experimental results.

‡ Boronic esters **425n-p** and **425s** were acquired from the Aggarwal boronic ester database

Table 30. Comparison of calculated relative energies for C–Si and C–B bond-breaking TSs with experimental ratios of vinyl boronic ester and vinyl silane for substrates **425n**, **425o**, **425q**, **425s** and **425t**



Entry	R =	$\Delta\Delta G^{\ddagger}$ (kcal/mol) C–Si / C–B	Experimental C–Si : C–B
1	Me **425t**	0 / 9.2	100 : 0[a]
2	*p*-$MeOC_6H_4$ **425n**	0 / 1.2	100 : 0
3	indolyl **425o**	0.2 / 0	53 : 47
4	*p*-$CF_3C_6H_4$ **425q**	1.4 / 0	0 : 100
5	styrenyl **425s**	5.6 / 0	0 : 100



TS(C–Si) for **425t**
$\Delta\Delta G^{\ddagger}$ = 0

TS(C–B) for **425t**
$\Delta\Delta G^{\ddagger}$ = 9.2 kcal/mol

Figure 8. C–Si and C–B bond-breaking TSs for substrate **425t**.

The results can be understood by considering the stabilisation of negative charge build-up at the carbon atom during the C–Si and C–B bond-breaking TSs. Evidently, this charge is better stabilised by boron relative to silicon, which is why aliphatic boronic esters favour the C–Si bond-breaking pathway to give the vinyl boronic ester products. Indeed, calculations showed that boron is better able to stabilise negative charge by 9.1 kcal/mol relative to silicon, which was demonstrated by comparing the relative energies of carbanions **466-B** and **466-Si**, which result from C–Si and C–B bond-breaking in the absence of a lithium countercation (Figure 9). On the other hand, for substrates that contain anion-stabilising groups, elimination takes place at the more Lewis acidic boron atom to give the vinyl silane products.

[*]Dr. Matt. N. Grayson performed the DFT calculations and generated the images depicted in Figures 8 and 9

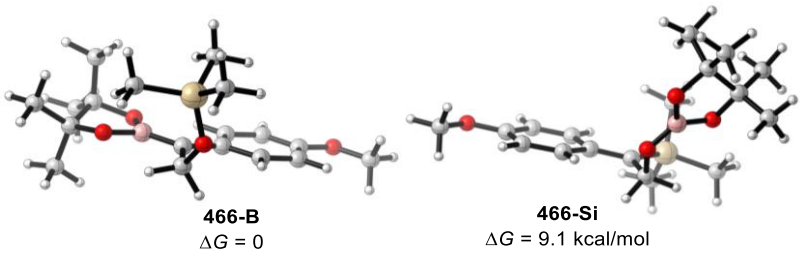
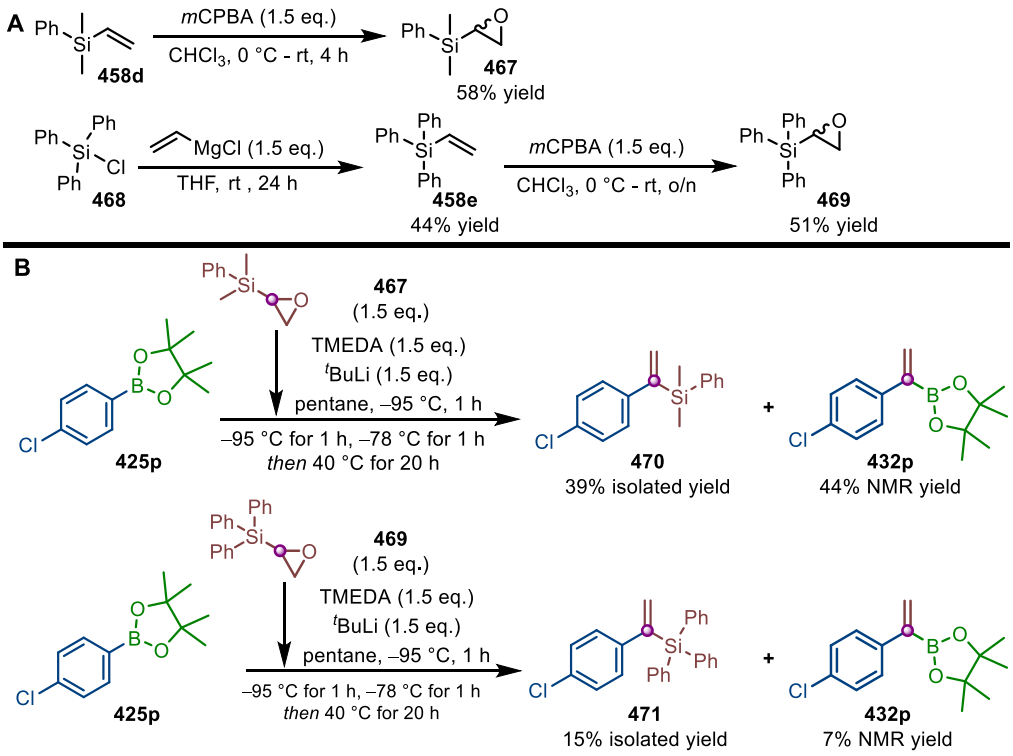


Figure 9. Carbanions **466-B** and **466-Si**

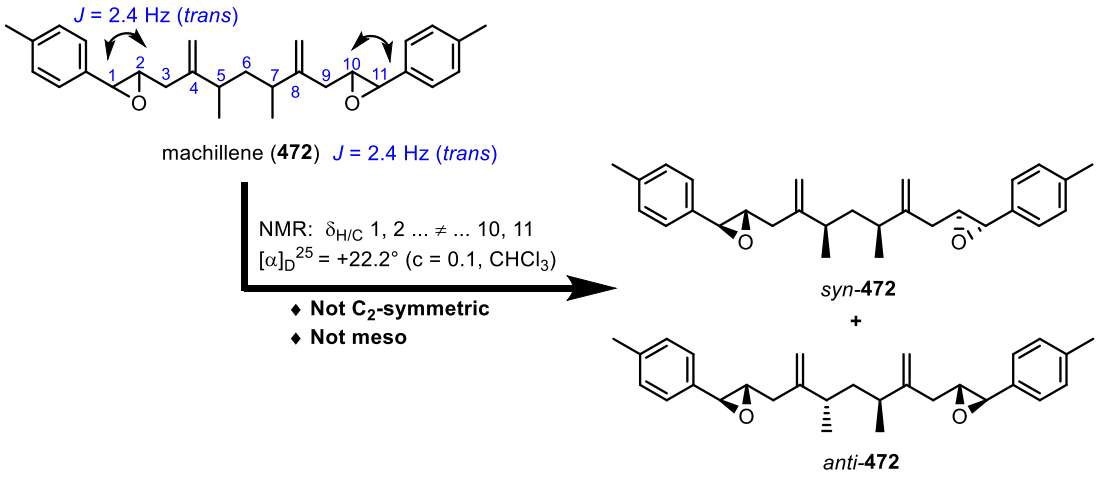
We wondered if increasing the electrophilicity of the silicon atom would influence the elimination step to favour the vinyl boronic ester product. To this end, phenyldimethyl and triphenyl epoxysilanes **467** and **469** were prepared by epoxidation of the corresponding vinyl silanes **458d** and **458e** (Scheme 92A). For the investigation, we elected to use substrate **425p**, which had previously given a clean reaction and a mixture of vinyl boronic ester and vinyl silane products when using epoxysilane **440a**. In the reaction with epoxysilane **467**, the phenyl substituent did indeed influence the regioselectivity to favour vinyl boronic ester product **432p** (44% NMR yield), however vinyl silane **470** was still isolated in a 39% yield (Scheme 92B). Unfortunately, epoxysilane **469** led to a messy reaction that resulted in a low yield of both products.



Scheme 92. A) Preparation of epoxysilanes **467** and **469**
B) Use of epoxysilanes **467** and **469** in the vinylidene homologation of **425p**

5.3.3. *Total Synthesis of the Proposed Structure of Machillene*

Having investigated the scope and mechanism of the vinylidene homologation reaction, we were keen to demonstrate its utility in a total synthesis. Machillene (**472**), a polyketide natural product isolated from the Taiwanese evergreen tree *machilus zuihoensis*, was selected as the synthetic target (Scheme 93).[170] We were attracted to this natural product as it displayed micromolar activity against HONE-1 and NUGC-3 cancer cell lines and because its relative stereochemistry remained unknown, apart from the epoxide groups, which had been assigned as *trans*-substituted based on the coupling constant (*J*) values for signals H-1 (*J* = 2.6 Hz) and H-11 (*J* = 2.6 Hz).[171] We were able to eliminate six of the possible eight diastereomers of **472** using the reported experimental data. From the ^{1}H and ^{13}C NMR data, we inferred that the molecule was not C_2-symmetric and, as **472** is optically active, could not be a meso compound. Therefore, the only stereoisomers that fit the reported data were *syn*- and *anti*-**472**.



Scheme 93. Structural elucidation of machillene

In order to distinguish between these diastereomers, we employed a method developed by Breit and co-workers, who had previously shown that the relative configuration of deoxypropionate motifs could be deduced by ^{1}H NMR spectroscopy.[172] Specifically, they showed that the chemical shift differences ($\Delta\delta$) between central methylene protons H_A and H_B were directly related to the relative configuration of the 1,3-related methyl substituents (Figure 10). This had been rationalised using conformational analysis, as molecules preferentially adopt conformations that avoid energetically destabilising *syn*-pentane interactions.[173] For example, diastereomers *syn*- and *anti*-**473** have a total of three conformations that avoid these *syn*-pentane interactions and, by considering the

symmetry of these conformers, the chemical shift differences between the two diastereomers can be justified. For instance, if R = R' then compound *anti*-**473** is C_2-symmetric, therefore H_A and H_B are chemically equivalent and have the same chemical shift ($\Delta\delta = 0$ ppm). As a rule, the authors found that the $\Delta\delta$ value for the *syn*-diastereomer was always greater than that of the *anti*-diastereomer, although the magnitude of this difference was dependent on the nature of substituents R and R'. We applied Breit's analysis to machillene and, as $\Delta\delta = 0$ ppm, we predicted that *anti*-**472** was the structure of the natural product.

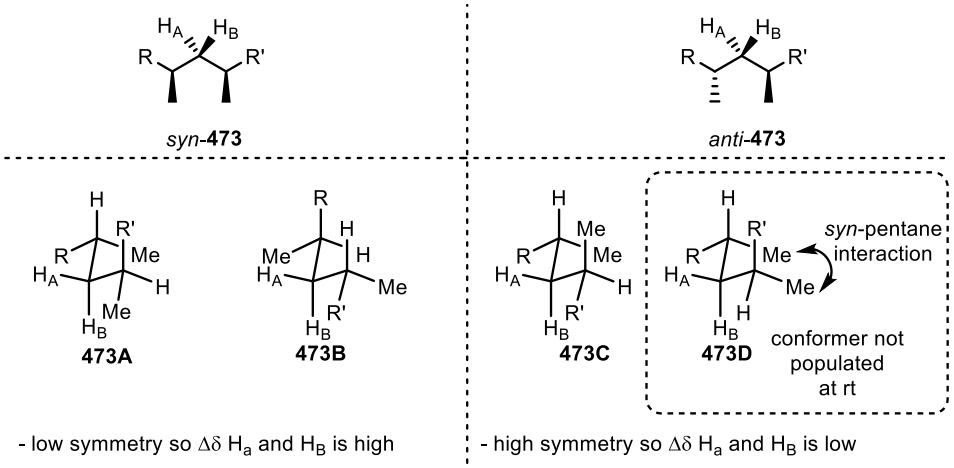
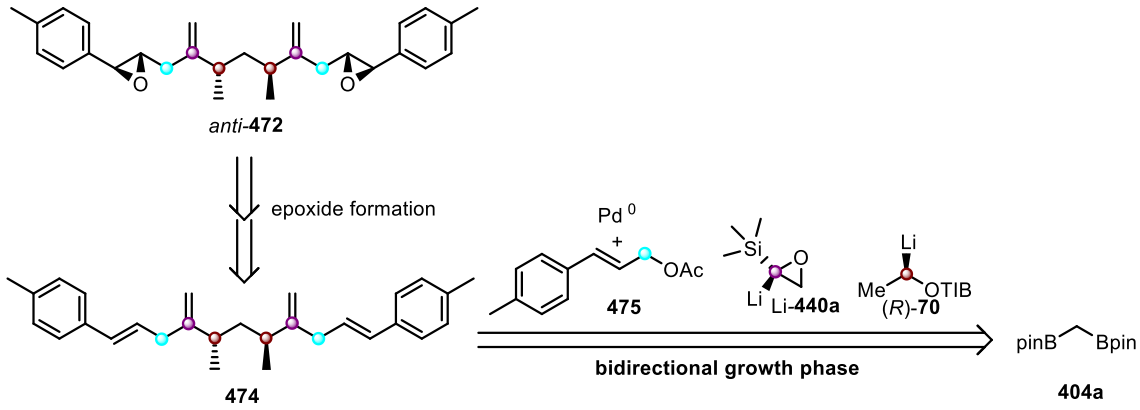


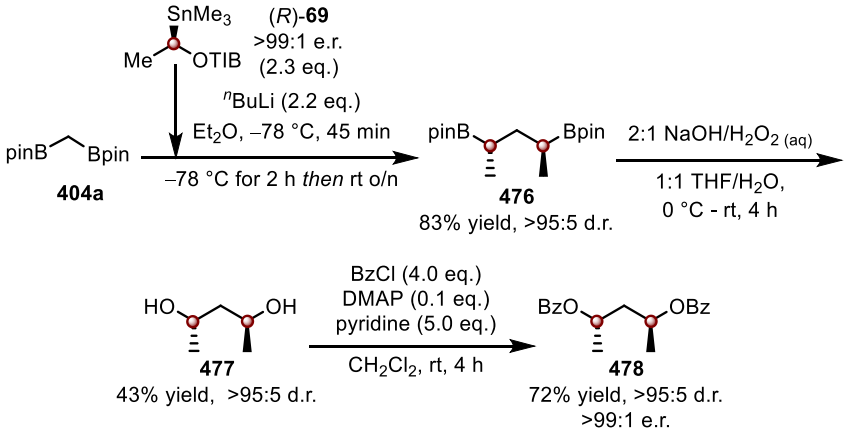
Figure 10. Relationship between configuration and chemical shift for deoxypropionate motifs

Having revised the structure of our target, we performed a retrosynthetic analysis (Scheme 94). It began with successive asymmetric epoxidation reactions from tetraene **474**. We envisaged accessing **474** using a bidirectional approach from diboronic ester **404a**, which consisted of homologations with lithiated TIB ester (*R*)-**70** and lithiated epoxysilane Li-**440a**, followed by a palladium-catalysed allylic cross-coupling reaction. If successful, this route would provide access to *anti*-**472** in just five steps from commercially available diboron **404a**, without the need for protecting groups.



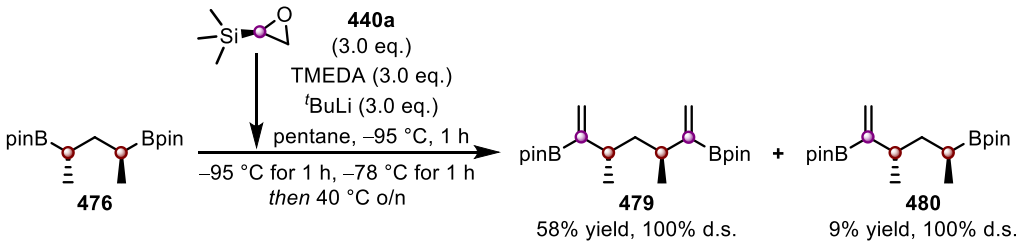
Scheme 94. Retrosynthetic analysis of *anti*-**472**

The synthesis began by homologation of **404a** with lithiated species (*R*)-**70**, which was generated by tin–lithium exchange from stannane (*R*)-**69**, using a modified procedure from our groups earlier report (Scheme 95).[174] An excess of lithiated species was used to ensure complete boronate complex formation, in order to maximise yield. Under these conditions, bis-boronic ester **476** was isolated in 83% yield and as a single detectable diastereomer. The enantiomeric ratio of **476** was found to be >99:1 after chiral HPLC analysis of bis-benzoate **478**, which was obtained using a sequence of oxidation and benzoylation.



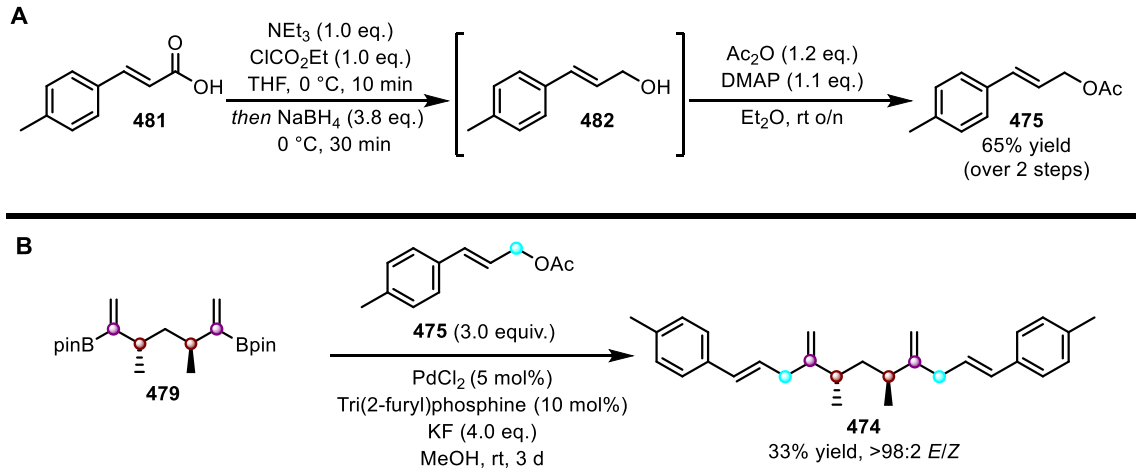
Scheme 95. Preparation of **476** and determination of its enantiomeric ratio (benzoyl = Bz, DMAP = dimethylaminopyridine)

The next step involved the vinylidene homologation of bis-boronic ester **476** (Scheme 96). Under standard reaction conditions (1.5 eq. of lithiated species Li-**440a** per boronic ester), desired bis-vinyl boronic ester **479** was obtained in 58% yield with complete diastereospecificity, along with mono-homologated product **480** (9% yield).



Scheme 96. Vinylidene homologation of **476**

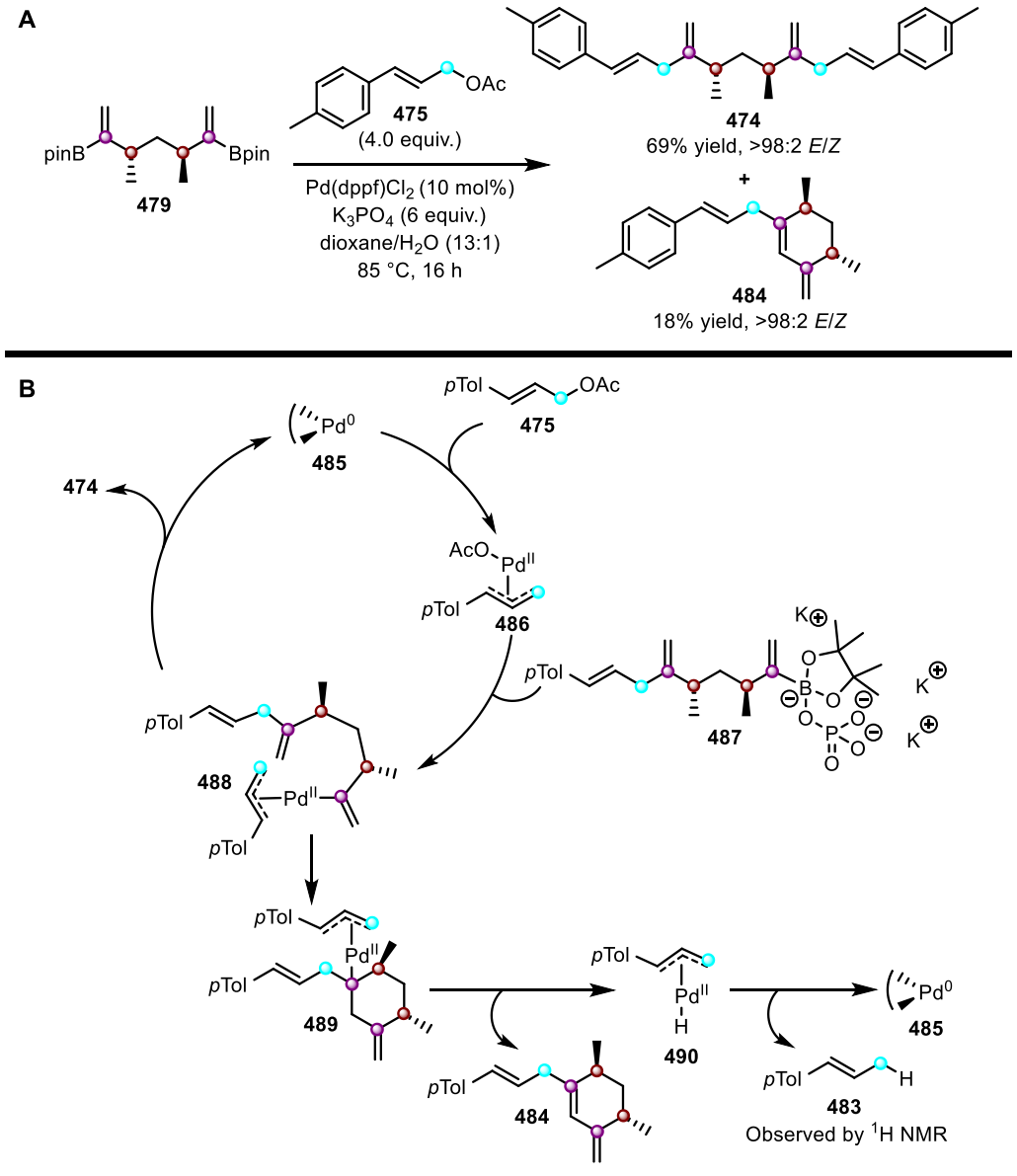
The next step of the synthesis was the palladium-catalysed cross-coupling of **479** and allylic acetate **475**. Using a procedure previously described by Breder and co-workers (Scheme 97A), **475** was easily prepared from cinnamic acid **481** in good yield.[175] To our knowledge, the coupling of an allylic acetate with a vinyl boronic ester had only been reported once before.[176] Under these conditions, desired tetraene **474** was obtained in just 33% yield, from what was a very messy reaction (Scheme 97B).



Scheme 97. A) Preparation of allylic acetate **475**
B) Palladium-catalysed allylic cross-coupling of **479** and **475**

After further assessment of the literature, we turned to Breder's conditions for the coupling of aryl boronic esters and allylic acetates.[175] Using a modified procedure, which utilised an excess of allylic acetate **475** relative to bis-vinyl boronic ester **479**, desired product **474** was obtained in a gratifying 69% yield (Scheme 98A). The reaction contained just three other species, remaining allylic acetate **475**, styrene **483** and side-product **484**, which was isolated in 18% yield. In order to account for side-product **484** we considered the mechanism of the reaction (Scheme 98B), the first cross-coupling cycle has been omitted for clarity. The catalytic cycle commences with oxidative addition of Pd catalyst **485** into allylic acetate **475** to give π-allyl complex **486**. Subsequent

transmetallation of **486** with vinyl boronate **487**, which is formed from potassium triphosphate and **479**, delivers vinyl palladium species **488**. We believe that this intermediate can undergo two competing reaction pathways; reductive elimination to deliver desired tetraene **474** or migratory insertion of the pendent alkene to give intermediate **489**. ß-Hydride elimination of **489** would give side-product **484** and palladium hydride **490**, which after reductive elimination gives styrene **483**, which was observed by ^{1}H NMR analysis of the crude reaction mixture.

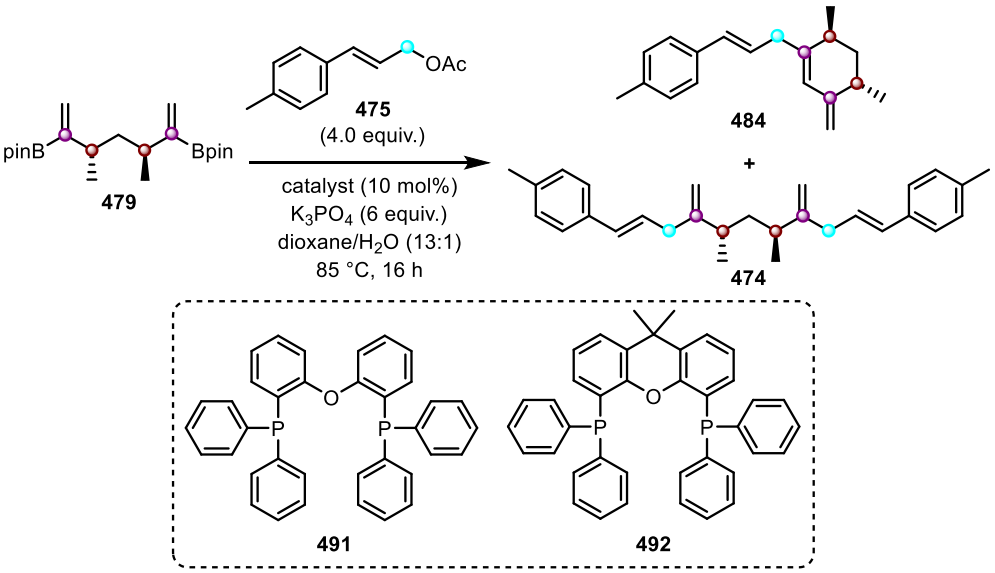


Scheme 98. A) Palladium-catalysed allylic cross-coupling using Breder's conditions B) Mechanistic proposal for the origin of triene **484**

(1,2-bis(diphenylphosphino)ferrocene (dppf))

In a bid to overcome the migratory insertion pathway, we considered modifying the diphosphine ligand (Table 31). We reasoned that, by increasing the bite angle (β_n) of the ligand, the rate of the desired reductive elimination pathway should be enhanced, relative to the migratory insertion pathway.[177] Firstly, DPEPhos **491** (Entry 2, β_n = 103°) was investigated, which delivered desired product **474** and **484** in a similar ratio and yield to the corresponding dppf catalyst (Entry 1, β_n = 99°). We wondered whether a much larger bite angle might be beneficial, and thus sought to employ Xantphos **492** (Entry 3, β_n = 111°) as the ligand for the reaction. The catalyst, which was formed by mixing ligand **492** and palladium diacetate in dioxane/H_2O at 60 °C, prior to addition of allylic acetate **475** and vinyl boron **479**,[178] was found to be inactive in this cross-coupling reaction. In light of these results, we decided to complete the total synthesis before exploring other catalytic systems.

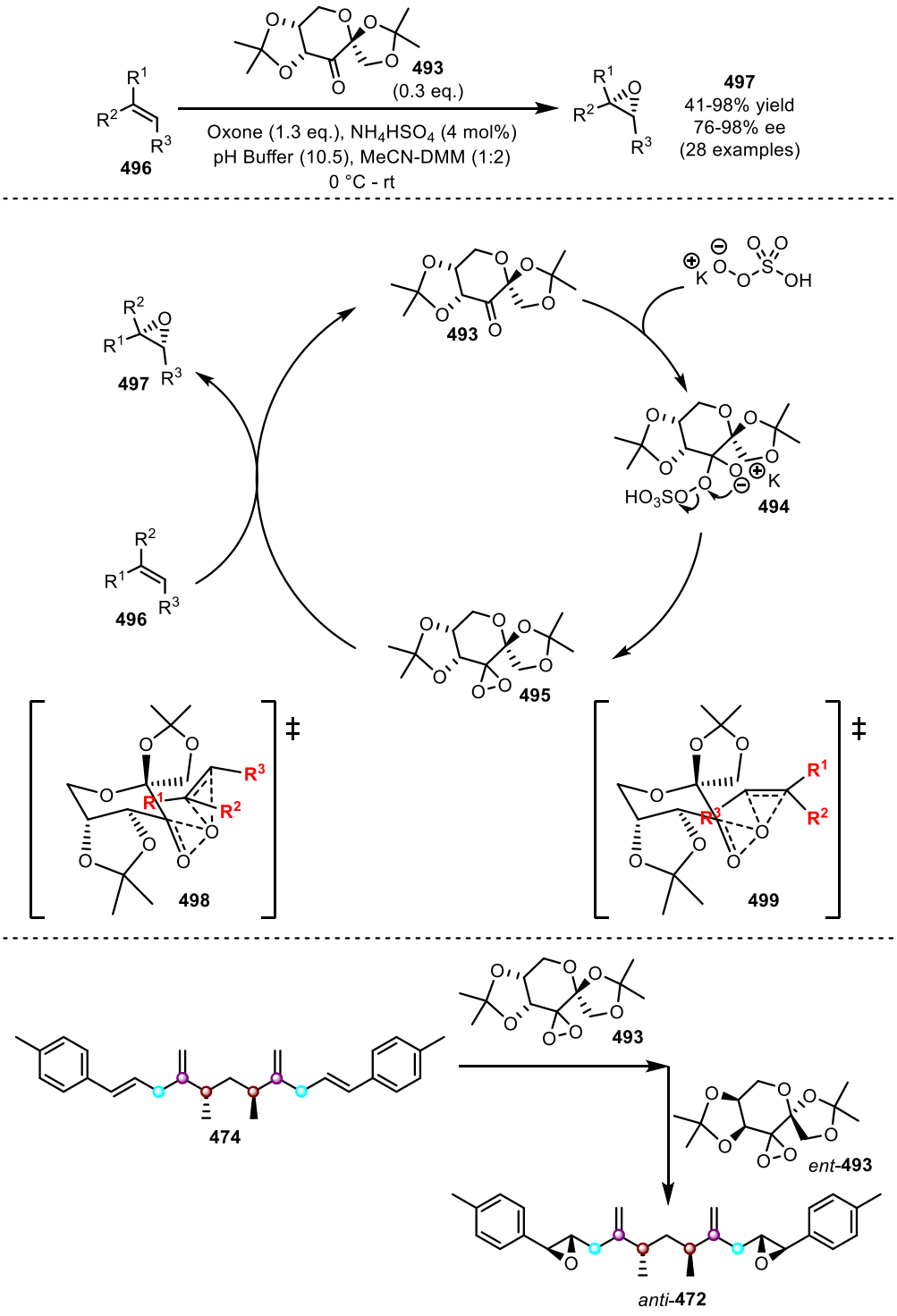
Table 31. Ligand screen for the allylic cross-coupling reaction of **475** and **479**. Values for the bite angle of diphosphine ligands were taken from the report of van Leeuwen and co-workers.[179]



Entry	Catalyst	Bite Angle (°)	NMR Yield 474 / 484[a]
1	$Pd(dppf)Cl_2 \bullet CH_2Cl_2$	99	70% / 19%
2	$Pd(DPEPhos)Cl_2$	103	69% / 25%
3	$Pd(OAc)_2$/XantPhos **492**	110	0% / 0%

[a]Determined by ^1H NMR analysis using CH_2Br_2 as an internal standard.

Having successfully developed a route to tetraene **474**, we came to the most challenging step of the synthesis, desymmetrisation of **474** in a regio- and stereoselective fashion. We initially considered the Shi epoxidation (Scheme 99) as, for this reaction, *trans*-disubstituted alkenes are known to give the corresponding epoxides in a highly stereoselective fashion.[180-181] The mechanism of the Shi epoxidation proceeds as follows, nucleophilic attack of potassium peroxymonosulphate (oxone) into ketone **493** gives tetrahedral intermediate **494**, which, under basic conditions, undergoes ring-closing to give dioxirane **495**. This reactive intermediate is attacked by alkene **496** to deliver enantioenriched epoxide **497** and regenerate catalyst **493**. Computational analysis has shown that the reaction proceeds preferentially through spiro transition state **498**, rather than planar transition state **499**, due to a stabilising interaction between the oxygen lone pair and the π^*-orbital of the alkene.[182] Further studies revealed that spiro transition state **498**, where R^1 is smaller than R^2, leads to the major stereoisomer of product **497**, whereas planar transition state **499** gives the minor stereoisomer *ent*-**497**. As both enantiomers of catalyst **493** are accessible, we hoped that successive epoxidation reactions with **493** and *ent*-**493** would provide target molecule *anti*-**472** directly. For our strategy to be successful, we required a regioselective reaction at the styrenyl double bonds over the 1,1-disubstituted alkenes.

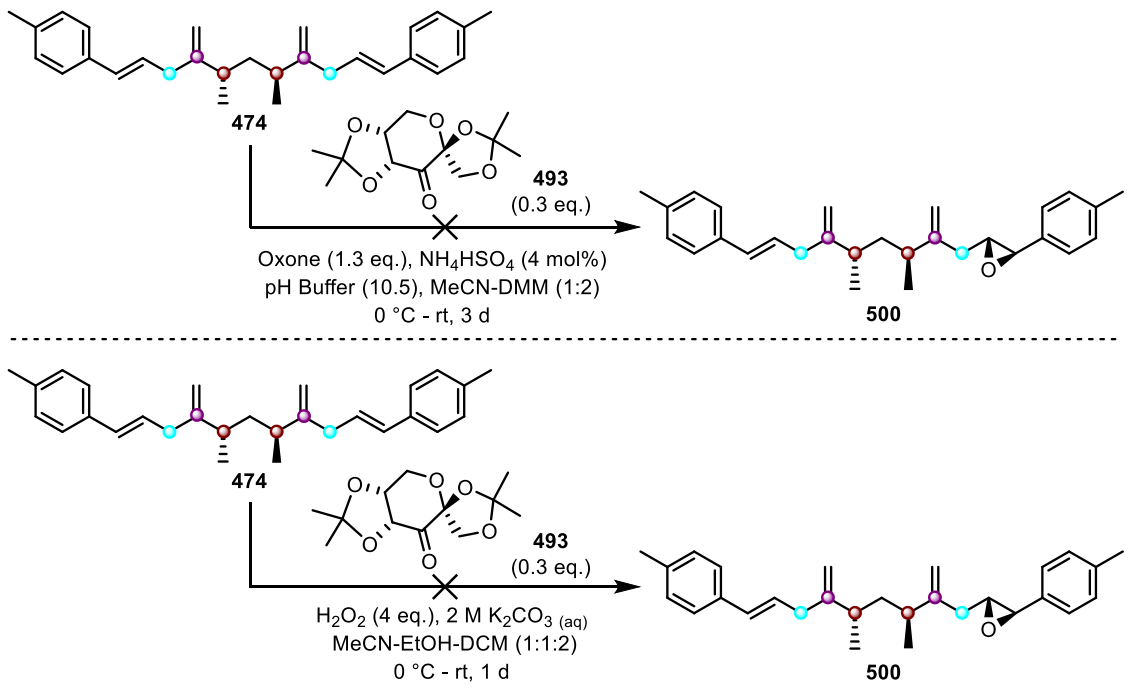


Scheme 99. Shi epoxidation reaction and the envisaged strategy to *anti*-**472**

(dimethoxymethane (DMM))

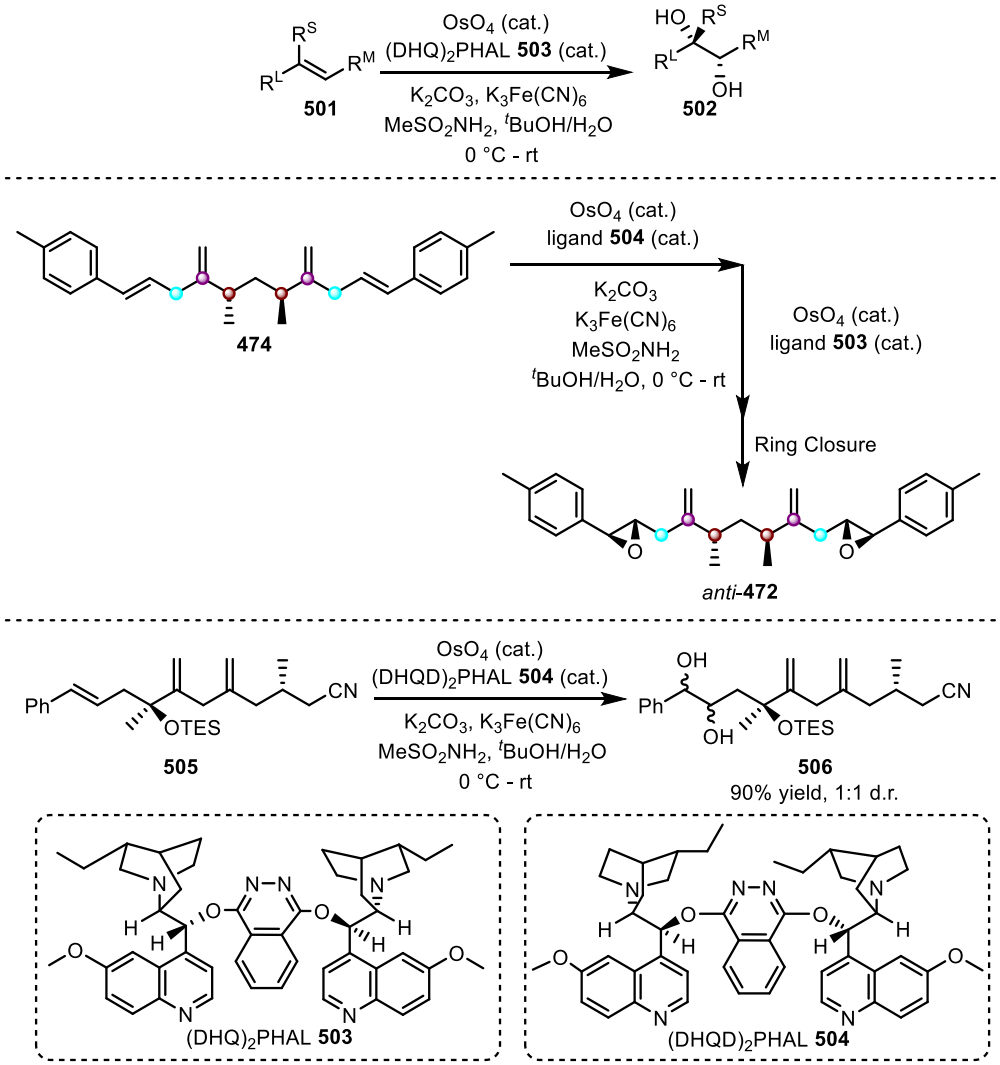
Unfortunately, upon subjecting tetraene **474** to standard Shi epoxidation conditions, no reaction was observed, even with extended reaction times and additional amounts of catalyst and oxone (Scheme 100). Likewise, an alternative procedure that used hydrogen

peroxide as the terminal oxidant did not furnish desired epoxide **500** and again starting material was identified as the major component of the reaction mixture.[183]



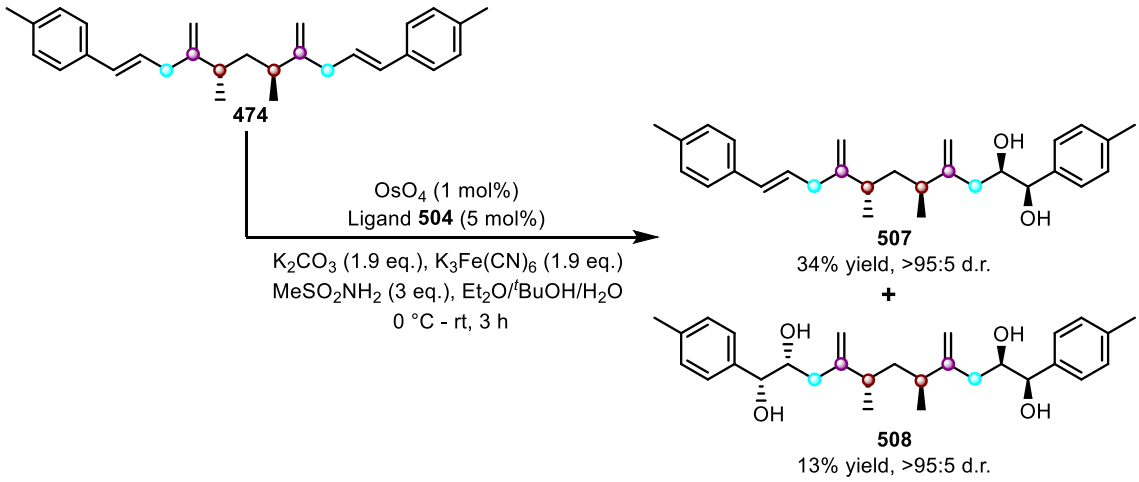
Scheme 100. Attempted Shi epoxidation of tetraene **474**

At this stage we elected to change our approach. We turned to the Sharpless dihydroxylation reaction (Scheme 101), which appealed as the diol products are generally obtained in excellent yield and with high stereoselectivity.[184] Furthermore, through choice of ligand (**503** or **504**) either stereoisomer of product can be accessed, which meant we could use a sequence of successive dihydroxylation reactions, followed by a ring-closing reaction, to access target molecule *anti*-**472**. We anticipated that the reactions would take place regioselectively at the desired styrenyl sites, due to favourable π-stacking interactions between the aromatic groups of *anti*-**472** with the phthalazine region of ligands **503** and **504**.[185] Indeed, Carter and co-workers had previously observed the regioselective dihydroxylation of a styrene in the presence of two 1,1-disubstituted alkenes.[186]



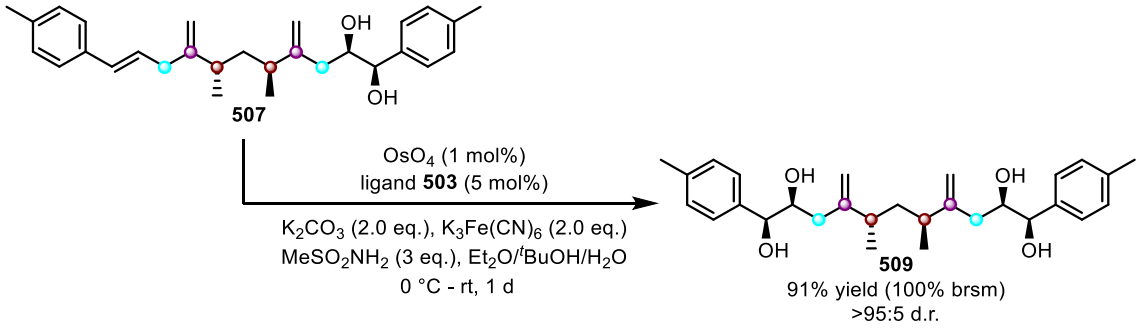
Scheme 101. Sharpless dihydroxylation of alkenes, envisaged strategy to *anti*-**472** and Carter's regioselective dihydroxylation of **505**

We were delighted to find that, upon submission of tetraene **474** to dihydroxylation conditions, desired diol **507** was isolated in 34% yield and as a single stereoisomer (Scheme 102). Tetraene **474** was recovered in 37% yield and bis-dihydroxylation product **508**, an anticipated artefact of this desymmetrisation reaction, was obtained in 13% yield. Efforts to improve the yield of **507** by increasing the amount of oxidant or extending the reaction time only resulted in greater amounts of **508**.



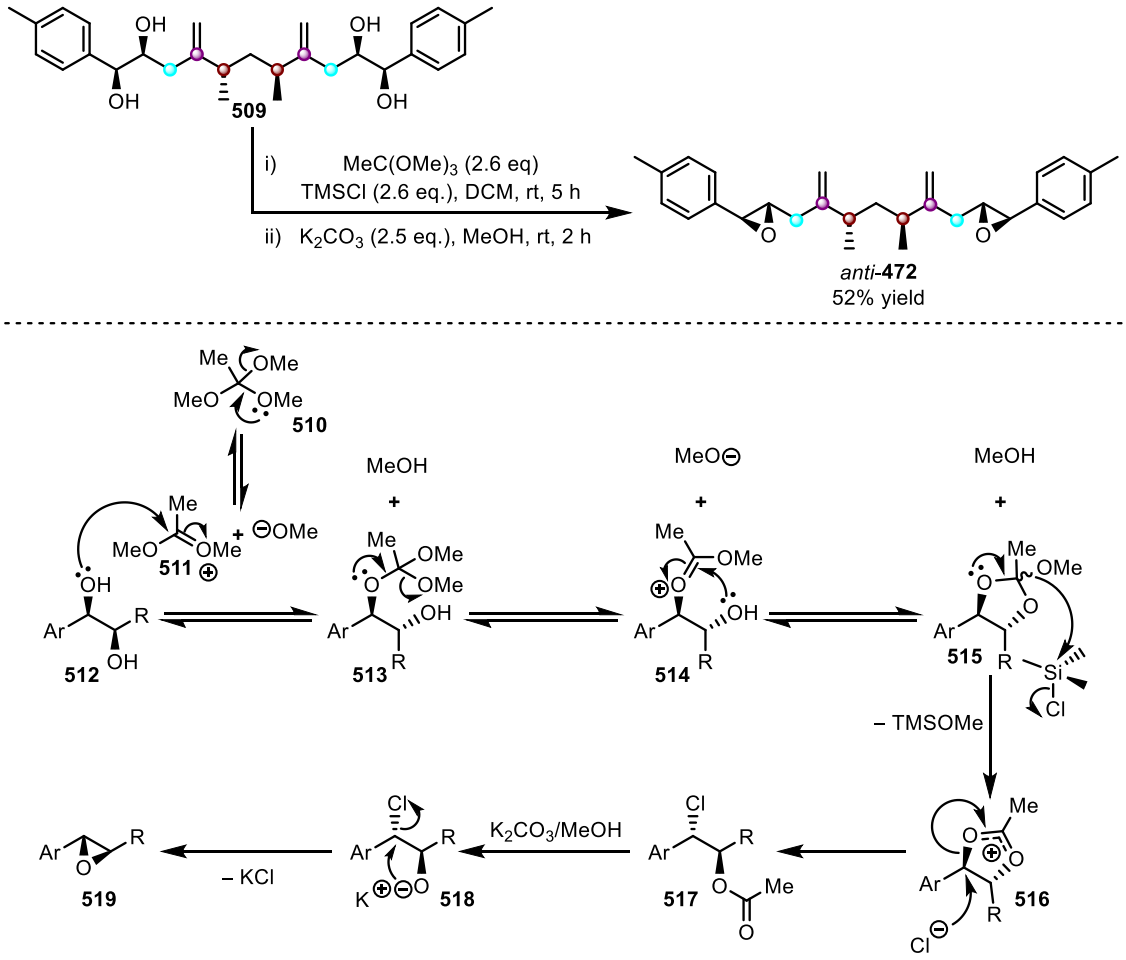
Scheme 102. Desymmetrising Sharpless dihydroxylation of **474**

We then conducted the second dihydroxylation reaction with *pseudo*-enantiomeric ligand **504** which gave tetraol **509** in 91% yield and with excellent diastereoselectivity (Scheme 103). Again, the reaction proceeded in an entirely regioselective fashion as the remaining mass balance was starting diol **507**, which was recovered.



Scheme 103. Sharpless dihydroxylation of **507**

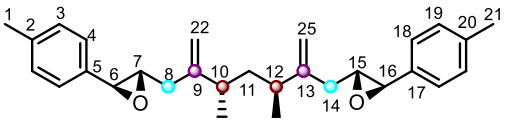
All that remained was ring-closing of the two diol groups to deliver target molecule *anti*-**472**. Using conditions previously described by Sharpless and co-workers, tetraol **509** delivered bis-epoxide *anti*-**472** in a pleasing 52% yield (Scheme 104).[187] The reaction proceeds by initial formation of orthoester **515**, which is converted into acetoxonium intermediate **516** upon reaction with TMSCl. Regioselective attack of chloride at the benzylic position of **516** delivers **517**, which after base mediated saponification and ring-closing provides epoxide product **519**.



Scheme 104. Synthesis of *anti*-**472** and mechanism of the ring-closing reaction

Upon conducting NMR analysis of *anti*-**472**, we discovered that our synthetic data differed markedly to that which was reported (Table 32). The extent of the differences led us to suspect that the issue was not in our stereochemical prediction, but likely a mistake made by the isolation team when determining the connectivity of the natural product.

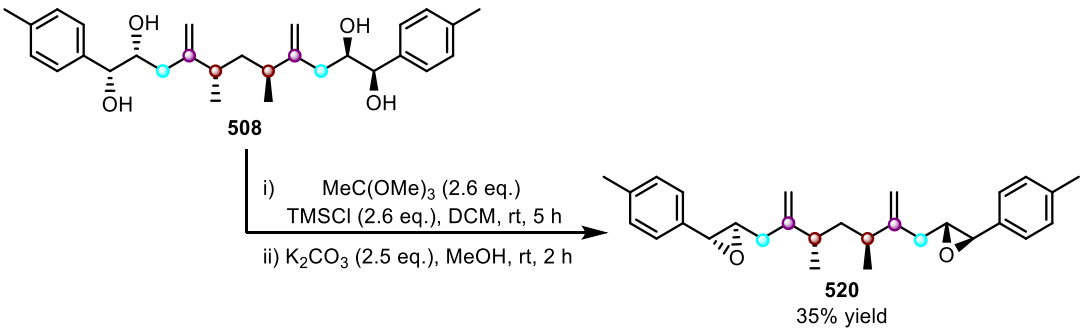
Table 32. Comparison of ^{1}H and ^{13}C NMR shifts for *anti*-**472** and those reported for machillene



anti-**472**

Position	Reported Data ^{1}H NMR ($CDCl_3$)	Synthetic Data ^{1}H NMR ($CDCl_3$)	Δδ (ppm)	Reported Data ^{13}C NMR ($CDCl_3$)	Synthetic Data ^{13}C NMR ($CDCl_3$)	Δδ (ppm)
1	2.32	2.34	0.02	21.0	21.3	0.3
2	n/a	n/a	n/a	141.5	138.0	3.5
3	7.09	7.15	0.06	129.2	129.3	0.1
4	7.13	7.15	0.02	126.6	125.6	1.0
5	n/a	n/a	n/a	135.2	134.6	0.6
6	2.90	3.60	0.70	60.9	59.1	1.8
7	2.72	3.04	0.32	57.1	62.1	5.1
8	2.00, 1.65	2.43, 2.25	1.03	41.1 or 40.7	36.3	4.4
9	n/a	n/a	n/a	143.2	150.1	6.9
10	2.95-2.83	2.24	0.65	37.4 or 36.9	38.3	1.4
11	1.81	1.51	0.39	41.1	41.0	0.1
12	2.95-2.83	2.24	0.65	37.4 or 36.9	38.3	1.3
13	n/a	n/a	n/a	143.6	150.1	6.5
14	2.00, 1.65	2.43, 2.25	1.03	61.2	36.3	4.8
15	2.83	3.06	0.23	57.6	62.1	4.5
16	3.09	3.60	0.51	41.1 or 40.7	59.0	2.1
17	n/a	n/a	n/a	135.2	134.6	0.6
18	7.13	7.15	0.02	126.6	125.6	1.0
19	7.09	7.15	0.06	129.2	129.3	0.1
20	n/a	n/a	n/a	141.5	138.0	3.5
21	2.32	2.34	0.02	21.0	21.3	0.3
22	4.92, 4.85	4.89, 4.87	0.03	113.6 or 113.1	110.8	1.3
23	1.30	1.01	0.29	21.7	20.4	1.3
24	1.30	1.01	0.29	22.7	20.4	2.3
25	5.07, 4.95	4.89, 4.85	0.30	113.6 or 113.1	110.8	2.8
			Tot = 6.62 Avg = 0.35 std dev = 0.32			Tot = 57.6 Avg = 2.3 std dev = 2.1

To further convince ourselves that the connectivity, rather than the stereochemistry, of machillene had been misassigned, we prepared C_2-symmetric diastereomer **520** by ring-closing of tetraol **508** (Scheme 105). As anticipated, **520** produced NMR data very similar to *anti*-**472** (see page 228 for NMR assignments).



Scheme 105. Conversion of C_2-symmetric tetraol **508** into **520**

We concluded that the isolation team had misassigned the structure of machillene and sought to identify the correct structure and validate it synthetically. At this stage, it is worth noting that we had achieved our main objective, which was to utilise the vinylidene homologation reaction in the synthesis of a complex molecule.

5.3.4. *Structural Reassignment of Machillene and Synthesis of Revised Structure* **523a**

Unfortunately, the isolation team had not provided copies of ^{1}H and ^{13}C NMR spectra and our attempts to correspond with them were unsuccessful, which made the structural reassignment of machillene a challenging prospect. However, after examining Table 32, we identified that the chemical shifts of the epoxide signals H-6 and H-16 for the synthetic material were considerably more down-field than those that were reported for machillene. After searching the literature, it was apparent that the epoxide groups of machillene were much more likely to be allylic than benzylic. For example, the ^{1}H NMR signals for the epoxide of literature compounds **521** ($CDCl_3$)[188] and **522** (C_6D_6)[189] were 3.30, 3.23 ppm and 2.98, 2.68 ppm, respectively, a good match to those reported for machillene (Figure 11). In addition, after searching the literature for styrenyl epoxides, the chemical shift for the benzylic signal was generally found to be in the range of 3.50–3.90 ppm, significantly more down-field than the epoxide signals reported for machillene. Considering these observations, we wondered whether the correct structure of the natural product might be **523a**.

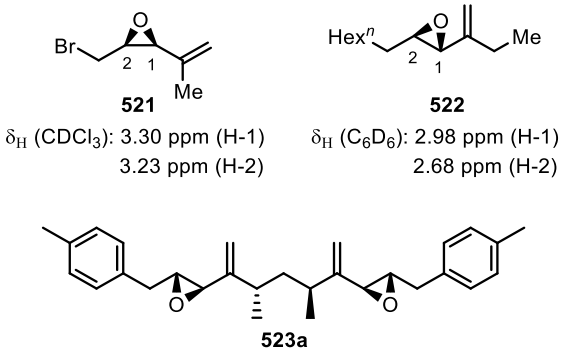


Figure 11. Allylic epoxides **521**, **522** and possible structure **523a**

The possibility that **523a** could be the correct structure of machillene was explored using ACD iLab*, an NMR prediction software provided by the Royal Society of Chemistry

*iLab NMR prediction was performed by Prof. Craig Butts

(Figure 12). This software predicts the ^{1}H NMR data of a structure by comparing it with a database of similar compounds. The predicted data is then overlaid with the reported data to give a probability that the structure in question would exhibit the reported NMR data. When *anti*-**472** was subjected to this analysis, the probability of a match with the reported data of machillene was just 0.28. However, when **523a** was investigated, the probability of a match was 0.81, which is classed as an excellent fit.

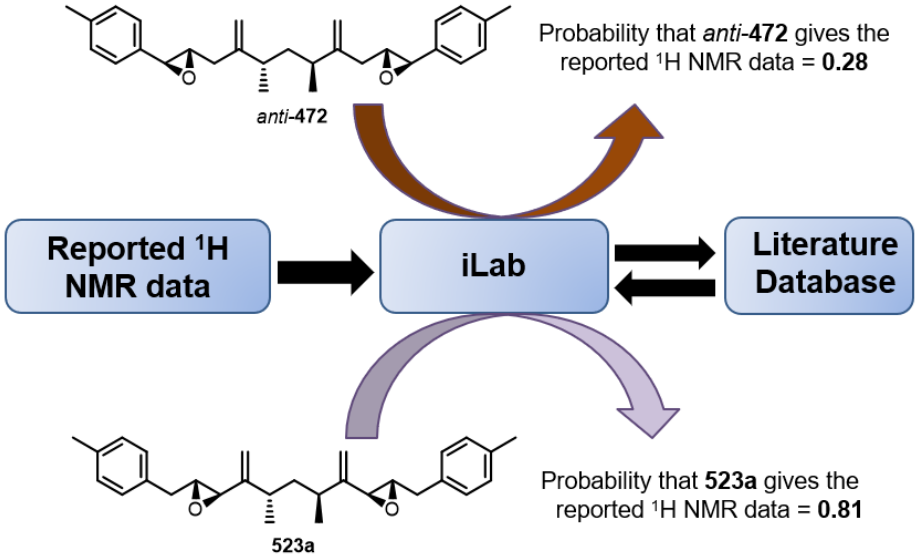
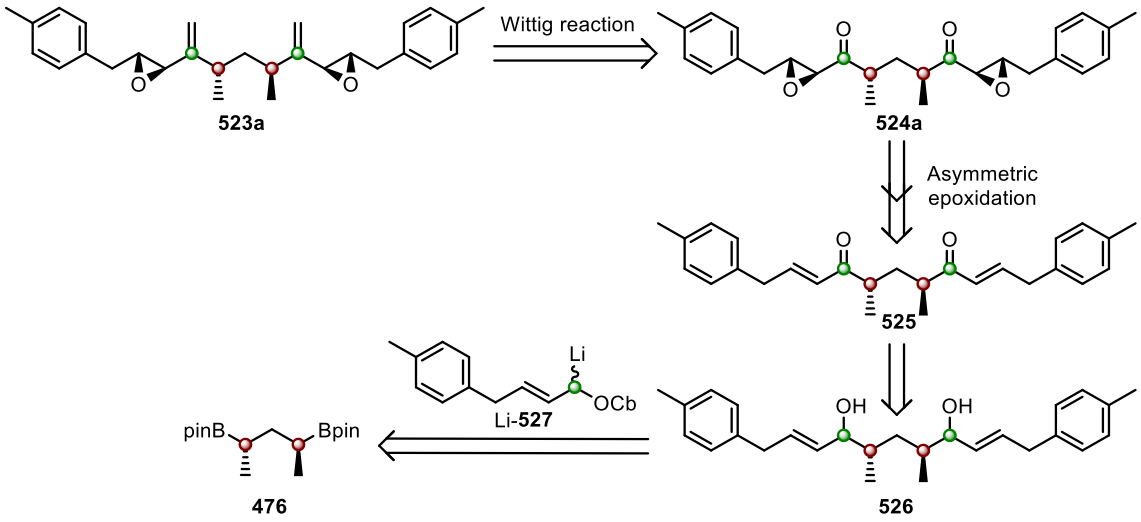


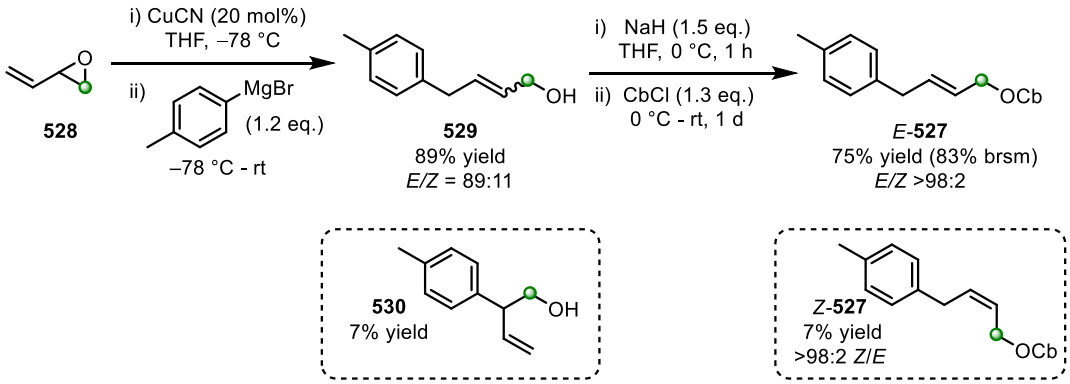
Figure 12. iLab analysis of *anti*-**472** and **523a**

The results of the iLab analysis gave us confidence that **523a** was indeed the structure of machillene and encouraged us to conduct a chemical synthesis. Our retrosynthetic analysis began with a Wittig olefination reaction to give bis-epoxide **524a**, which would be prepared from diketone **525**, through sequential asymmetric epoxidation reactions (Scheme 106). Diketone **525** would be synthesised by oxidation of bis-allylic alcohol **526**, which we envisaged preparing through a lithiation–borylation–oxidation reaction between lithiated allylic carbamate Li-**527** and bis-boronic ester **476**.



Scheme 106. Retrosynthetic analysis of **523a**.

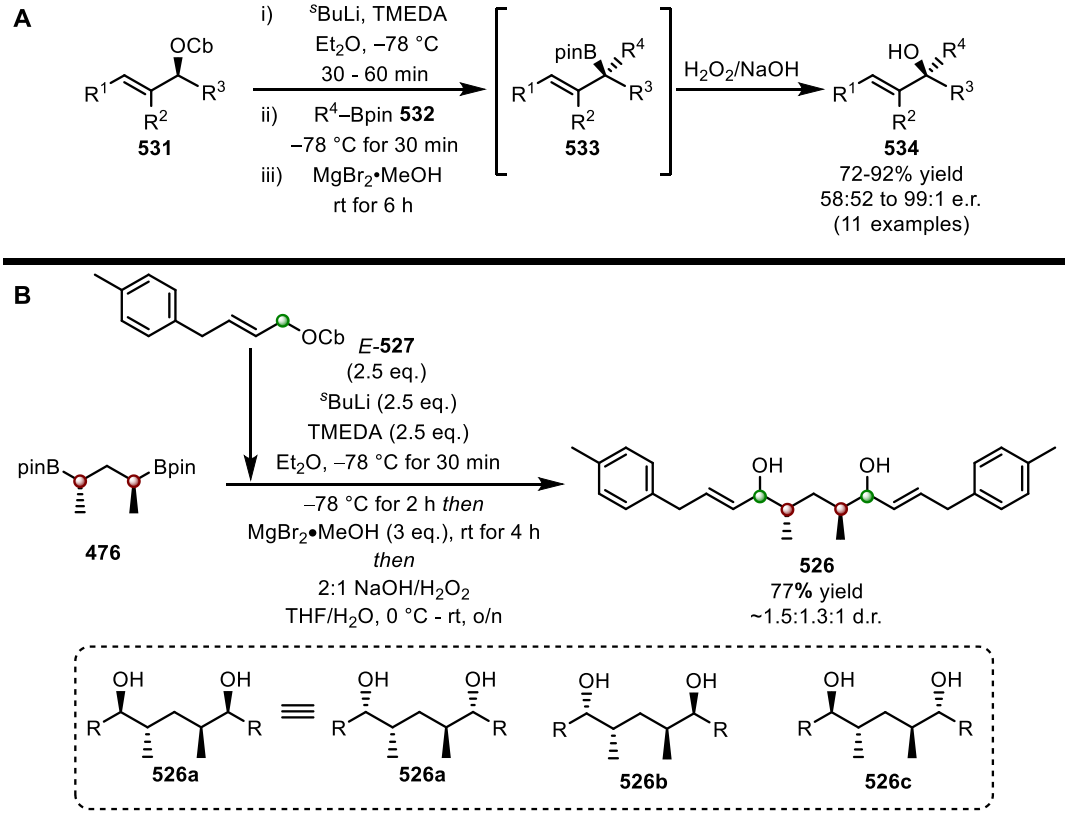
We began with preparation of allylic carbamate *E*-**527**, which was achieved in two steps from epoxide **528** (Scheme 107).[190] Treatment of **528** with *p*-tolymagnesium bromide in the presence of catalytic copper cyanide delivered allylic alcohol **529** in 89% yield with moderate stereoselectivity (*E*/*Z* = 89:11), as well as regioisomeric product **530**, which was obtained in 7% yield. Upon carbamoylation of allylic alcohol **529**, we were pleased to find that *E*- and *Z*-**527** could be separated by column chromatography and the desired product *E*-**527** was obtained in 75% yield.



Scheme 107. Preparation of allylic carbamate *E*-**527**

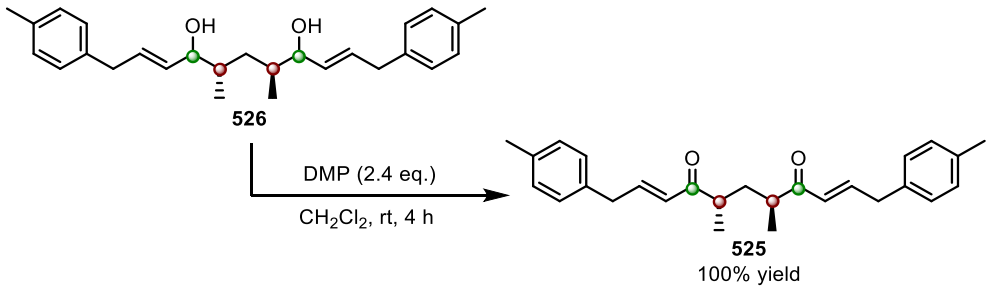
The next step was the lithiation–borylation reaction between allylic carbamate *E*-**527** and bis-boronic ester **476**. The lithiation–borylation of secondary allylic carbamates **531** has been previously reported by our group (Scheme 108A).[113] In general, the allylic alcohol products **533** were obtained in excellent yield. We anticipated that this procedure would be amenable to primary allylic carbamate *E*-**527** (Scheme 108B). Indeed, subjection of *E*-**527** to the reaction delivered the desired bis-allylic alcohol **526** in 77% yield as a

1.5:1.3:1.0 mixture of diastereomers. **526a** was expected to be the major diastereomer, which was confirmed upon ^{1}H NMR analysis of the product mixture. We were unable to distinguish between C_2-symmetric diastereomers **526b** and **526c** but, at this time, the diastereomeric ratio was inconsequential as we planned to destroy the stereochemistry in the subsequent step.



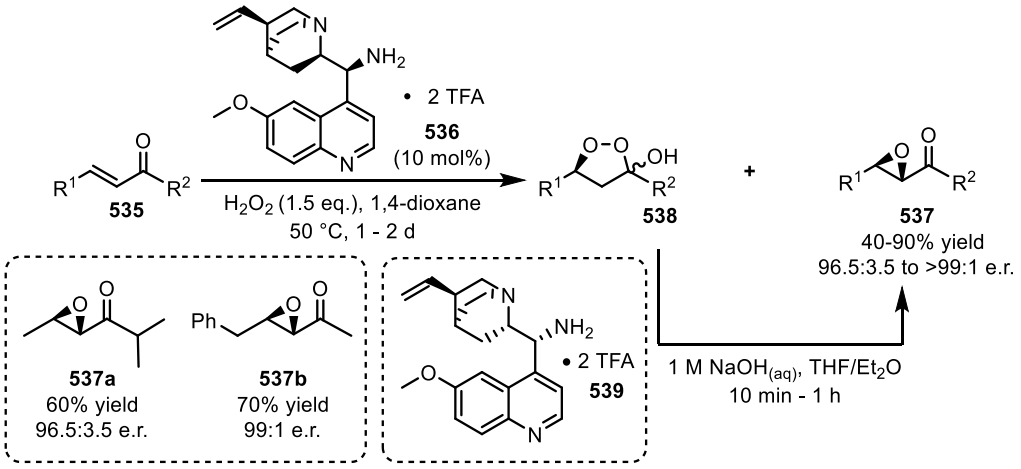
Scheme 108. A) Lithiation–borylation of secondary allylic carbamates
B) Preparation of bis-allylic alcohol **526**

Oxidation of the diastereomeric mixture of **526** with Dess-Martin periodinane (DMP) gave diketone **525** in quantitative yield (Scheme 109).



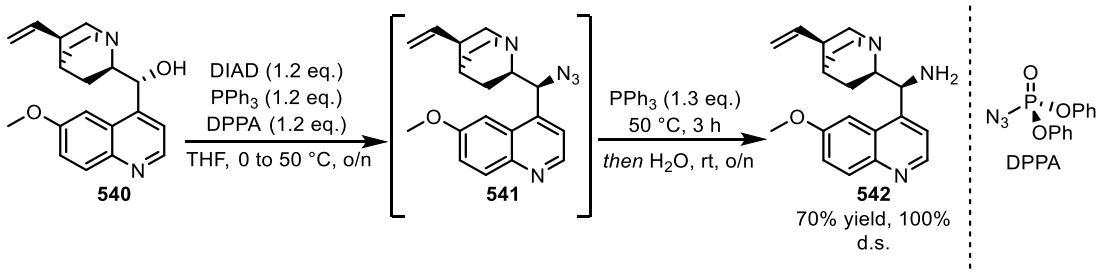
Scheme 109. Synthesis of diketone **525**

With diketone **525** in hand, we had arrived at the key step of the synthesis, the desymmetrising and stereoselective nucleophilic epoxidation reaction. After examining the literature, we were drawn to the procedure of List and co-workers, who had reported the enantioselective epoxidation of enones under chiral amine catalysis (Scheme 110).[191] The authors had demonstrated that treatment of enones **535** with hydrogen peroxide in the presence of cinchona amine catalyst **536** delivered the corresponding epoxides **537** and peroxyhemiketals **538**. It was found that, upon basic work-up, **538** could be converted to the epoxide products **537**, which were typically obtained in high yields and enantioselectivities. We were encouraged by two specific examples from List's study, **537a** that contained ß-branching and **537b**, which contained a phenyl substituent out of conjugation with the enone group. These two substrates suggested that diketone **525** might be a competent reaction partner. The authors had also demonstrated that the reaction could be performed with pseudoenantiomeric catalyst **539** to deliver the enantiomeric epoxide products *ent*-**537**. This suggested that we might be able to use successive epoxidation reactions to access intermediate **524a**, the precursor to revised target **523a**.



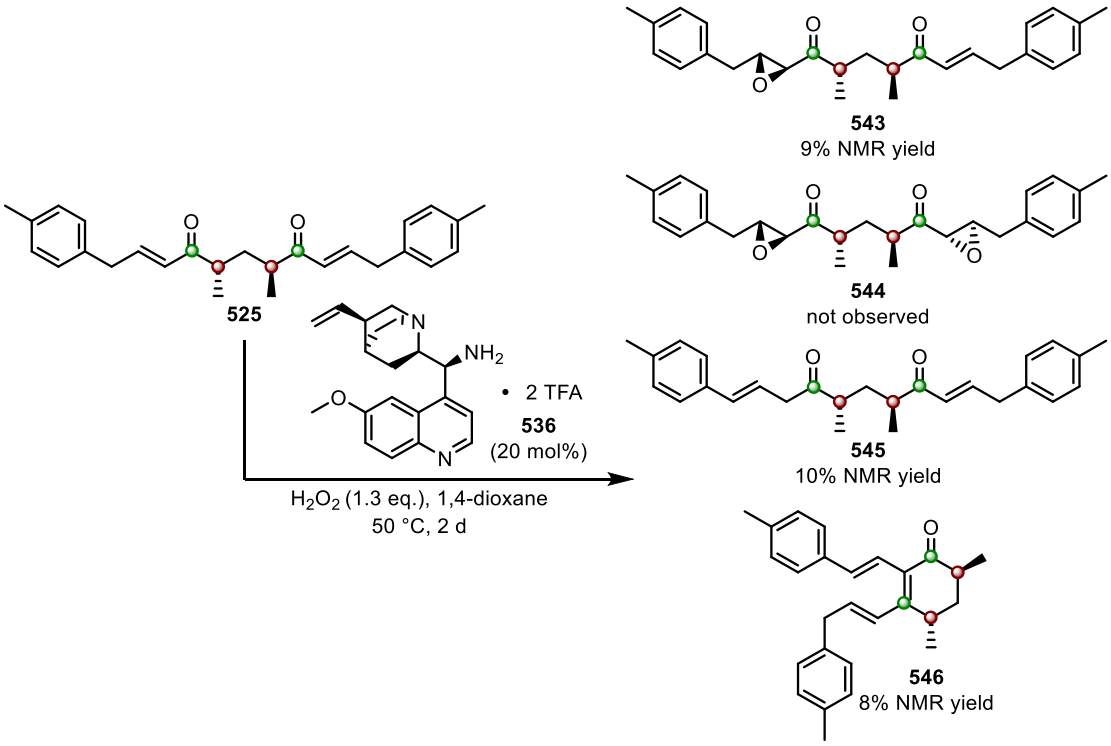
Scheme 110. Cinchona amine catalysed enantioselective epoxidation of enones

Catalyst **536** was prepared from quinine (**540**) using the procedure described by List and co-workers (Scheme 111).[191] Mitsunobu reaction of **540** with diphenylphosphorylazide (DPPA) delivered intermediate azide **541**, which was subject to a Staudinger reduction to give primary amine **542** in 70% yield over the two steps. Amine **543** was converted to catalyst **536** by treatment with two equivalents of trifluoroacetic acid (TFA) immediately prior to use in the epoxidation reaction.



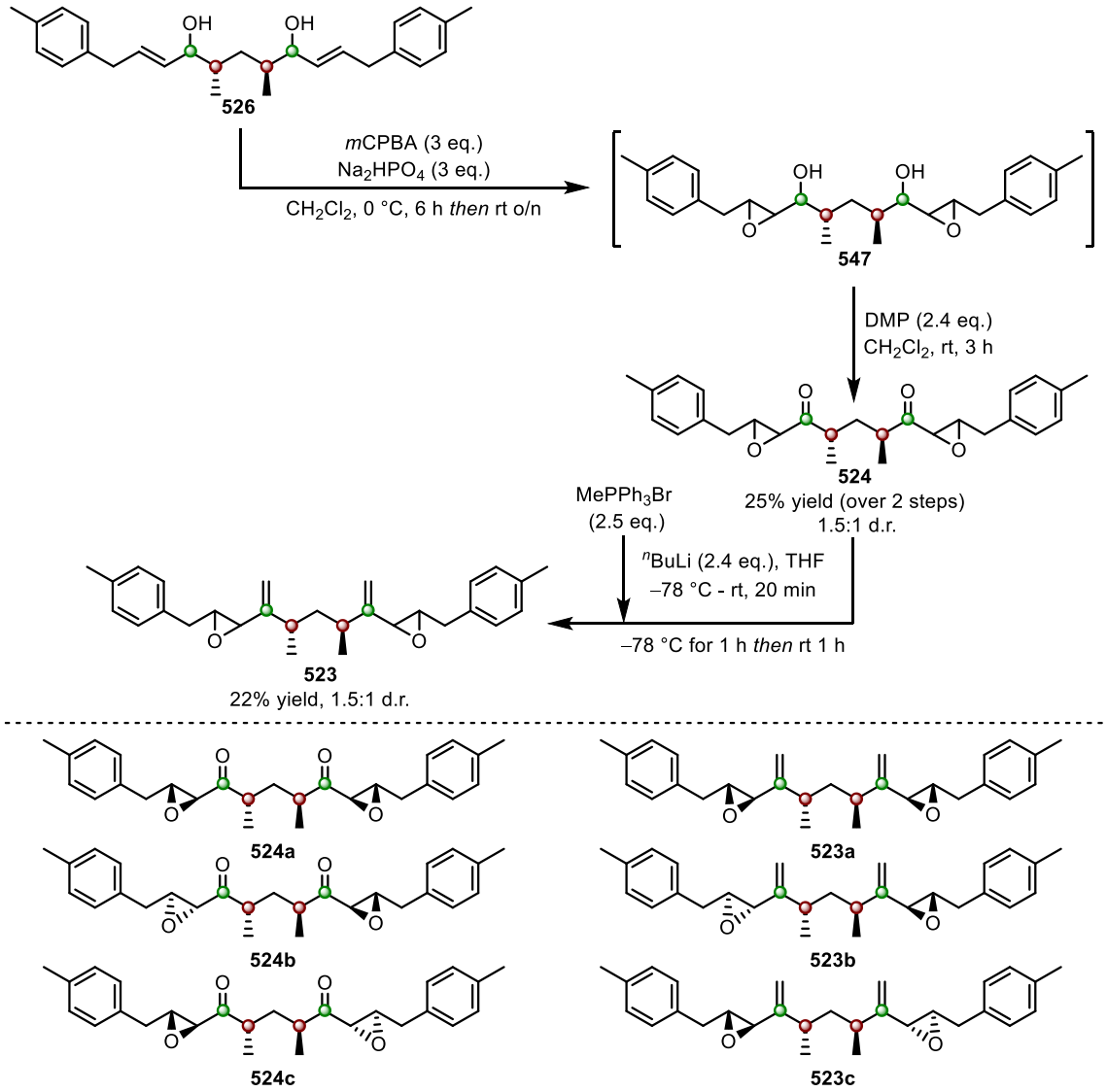
Scheme 111. Preparation of primary amine **542**

We were concerned that the hydroxide work-up described in List's report might lead to epimerisation of the stereocentres of epoxide product **543** and therefore decided to neglect this additional step. Unfortunately, subjection of diketone **525** to the conditions reported by List and co-workers resulted in a messy reaction (Scheme 112). Desired mono-epoxide **543** was observed in 9% NMR yield, but could not be separated from starting diketone **525**. There was no evidence for bis-epoxidation product **544**, but the other major components of the crude reaction mixture were identified as **545**, the product of double bond isomerisation, and enone **546**, the product of an intramolecular aldol reaction of **545**. The double-bond isomerisation was surprising, considering that List *et al.* were able to isolate **537b** in high yield. We reasoned that this isomerisation pathway would be difficult to overcome and decided to alter our route to **523a**.



Scheme 112. Attempted asymmetric nucleophilic epoxidation of **525**

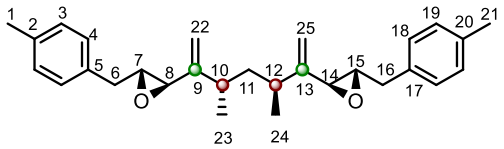
Rather than spending more time to identify a stereoselective synthesis, we decided we would first confirm that revised target **523a** was indeed the correct structure of machillene. We envisaged that performing a sequence of epoxidation, oxidation and Wittig olefination on bis-allylic alcohol **526** would provide our target as a mixture of three diastereomers **523a**, **523b** and **523c**. We reasoned that we should be able to identify target **523a** from this product mixture by NMR analysis, on the basis that **523b** and **523c** are C_2-symmetric and would give half the number of signals as **523a**. With this, bis allylic alcohol **526** (1.5:1.3:1.0 mixture of **526a**, **526b** and **526c**) was treated with *m*CPBA to give bis-epoxide **547** (Scheme 113). The crude product was oxidised directly with DMP to give bis-epoxyketone **524** in 25% yield as a mixture of two diastereomers, **524a** and **524b** or **524a** and **524c**. Desired product **524a** was identified as the major species by NMR analysis. It is likely that one of the C_2-symmetric diastereomers was removed during purification by column chromatography. The mixture of bis-epoxyketone diastereomers was then subject to a Wittig reaction with the ylide derived from methyltriphenylphosphonium bromide, which gave target molecule **523** in 22% yield as a 1.5:1 mixture of diastereomers **523a** and **523b**, or **523a** and **523c**.



Scheme 113. Synthesis of target molecule **523a**

As expected, we were able to identify the NMR signals of **523a** from the product mixture (Table 33). Unfortunately, ^{1}H and ^{13}C NMR analysis revealed that our structural reassignment of machillene was incorrect. While the ^{1}H NMR data for the allylic epoxide signals of **523a** were a good match to the reported data, there were still significant deviations between the two sets of data for other parts of the molecule. For example, signals H-6, H-10, H-11, H-12, H-16, H-23, H-24 and H-25 for **523a** deviated from the respective signals from the reported data by >0.3 ppm.

Table 33. Comparison of ^{1}H and ^{13}C NMR shifts for **523a** and those reported for machillene.



523a

Position	Reported Data ^{1}H NMR ($CDCl_3$)	Synthetic Data ^{1}H NMR ($CDCl_3$)	Δδ (ppm)	Reported Data ^{13}C NMR ($CDCl_3$)	Synthetic Data ^{13}C NMR ($CDCl_3$)	Δδ (ppm)
1	2.32	2.32	0	21.0	21.2	0.2
2	n/a	n/a	n/a	141.5	136.6	4.9
3	7.09	7.11	0.02	129.2	129.4	0.2
4	7.13	7.11	0.02	126.6	129.0	2.4
5	n/a	n/a	n/a	135.2	134.0	1.2
6	2.00, 1.65	2.92,2.76	2.03	41.1 or 40.7	38.5	2.2
7	2.72	2.87	0.15	57.1	61.7	0.8
8	2.90	3.10	0.20	60.9	58.2	2.7
9	n/a	n/a	n/a	143.2	149.9	6.7
10	2.95-2.83	2.16	0.73	37.4 or 36.9	34.9	2.0
11	1.81	1.37	0.44	41.1	41.5	0.4
12	2.95-2.83	2.11	0.78	37.4 or 36.9	34.7	2.7
13	n/a	n/a	n/a	143.6	149.8	6.2
14	3.09	3.04	0.05	61.2	57.9	3.3
15	2.83	2.85	0.02	57.6	61.6	4.0
16	2.00, 1.65	2.92,2.76	2.03	41.1 or 40.7	38.3	2.8
17	n/a	n/a	n/a	135.2	133.9	1.3
18	7.13	7.11	0.02	126.6	129.0	0.2
19	7.09	7.11	0.02	129.2	129.4	0.2
20	n/a	n/a	n/a	141.5	136.4	5.1
21	2.32	2.32	0	21.0	21.2	0.2
22	4.92, 4.85	4.98	0.19	113.6 or 113.1	109.4	3.7
23	1.30	0.98	0.32	21.7	21.0	0.7
24	1.30	0.87	0.43	22.7	20.4	2.3
25	5.07, 4.95	4.74	0.54	113.6 or 113.1	109.2	4.4
			Tot = 7.99 Avg = 0.32 std dev = 0.57			Tot = 60.8 Avg = 2.4 std dev = 2.0

After analysing Tables 32 and 33, we were surprised to find that the signals for H-23 and H-24 (the methyl substituents) deviated from the reported signals by ~0.3 ppm. After searching the literature, it was apparent that the methyl substituents must be located at the benzylic position. Furthermore, this modification was expected to have the desired effect of shifting methine signals H-10 and H-12 further down-field. Our next step was to consider all the possible structural isomers of **523** that contain benzylic methyl substituents; we only focused on structures for which both sides of the carbon skeleton were capped with the aromatic groups (Figure 13). We identified structural isomers **548-553**. We then compared the ^{1}H NMR of similar literature compounds to the reported data of machillene, which allowed us to discount isomers **548-552**. Isomer **553** was identified as the most likely structure of the natural product but, before conducting another synthesis, we desired additional evidence to support our hypothesis. We decided that iLab

alone would not give us the confidence to perform another synthesis and instead turned to quantum mechanics.

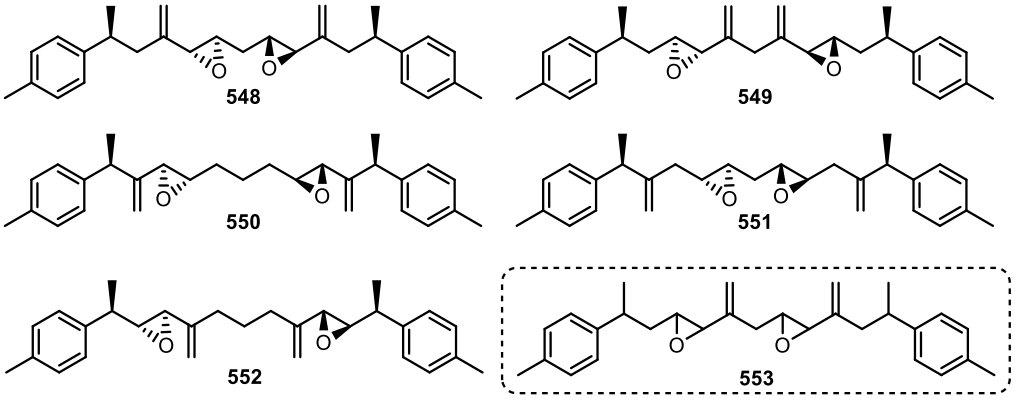


Figure 13. Structural isomers **548**-**553**

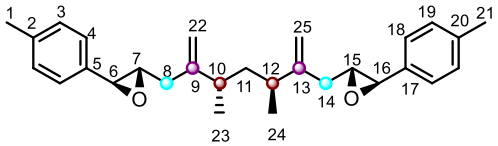
In order to accurately predict the NMR data for a specific molecule, the conformational landscape of said compound must be understood. However, determining which conformers are populated and to what extent is a non-trivial process, particularly for a flexible molecule such as **553**. Fortunately, using quantum mechanics, this challenge can be overcome. First, a search for the lowest energy conformers of the molecule is performed using the molecular mechanics (MM) ball and spring model. By accounting for the sum of bond stretching energy, bond bending energy, torsional angle rotation energy and electrostatic and Van der Waals interaction energies, the conformers that exist under a specified energy threshold can be determined.[192] Using DFT, the geometries of said conformers are minimised and their Gibbs free energies determined, which allows the Boltzmann-averaged population of conformers at room temperature to be calculated.[193] With this information, NMR parameters (chemical shifts, coupling constants, inter-proton distances) can be determined for a particular conformer. These parameters are then Boltzmann-averaged to give the averaged-NMR parameters for the molecule. The averaged-NMR parameters for **553** will be compared to the reported data for machillene, in order to assess whether **553** is the correct structure of the natural product and whether a synthesis should be conducted.

Before applying this quantum mechanical technique to **553**, we applied it to *anti*-**472** (Table 34) and **523a** (Table 35). By comparing the predicted NMR parameters to the synthetic data, we could quantify the average error per signal in the calculated data (*anti*-**472**: average (avg) $\Delta\delta_H$ = 0.16 ppm, avg $\Delta\delta_C$ = 1.4 ppm / **523a**: avg $\Delta\delta_H$ = 0.14 ppm, avg

$\Delta\delta_C$ = 1.1 ppm), which we could then use as guidelines when assessing the data of **553**. Furthermore, as the predicted NMR parameters were in good agreement with the synthetic data, for both *anti*-**472** and **523a**, these experiments provided us with confidence in the computational calculations.

Table 34. Comparison of predicted and synthetic ^{1}H and ^{13}C NMR shifts for *anti*-**472**

The DFT calculations were performed using Gaussian 09 at the B3LYP/6-31G(d)-IEFPCM($CHCl_3$) (geometry optimisation) or B3LYP/6-311G(d,p)-IEFPCM($CHCl_3$) (NMR calculation) level of theory.*



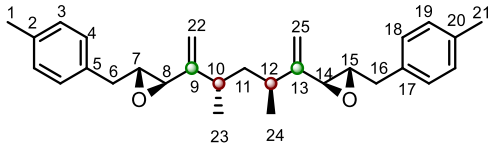
anti-**472**

Position	Predicted Data ^{1}H NMR ($CHCl_3$)	Synthetic Data ^{1}H NMR ($CDCl_3$)	Δδ (ppm)	Predicted Data ^{13}C NMR ($CHCl_3$)	Synthetic Data ^{13}C NMR ($CDCl_3$)	Δδ (ppm)
1	2.38	2.34	0.04	19.7	21.3	1.6
2	n/a	n/a	n/a	137.8	138.0	0.2
3	7.21	7.15	0.06	127.9	129.3	1.4
4	7.22	7.15	0.07	124.2	125.6	1.4
5	n/a	n/a	n/a	135.0	134.6	0.4
6	3.47	3.60	0.13	57.6	59.1	1.5
7	2.65	3.04	0.39	61.4	62.1	0.7
8	2.46, 1.95	2.43, 2.25	0.33	35.8	36.3	0.5
9	n/a	n/a	n/a	153.3	150.1	3.2
10	2.26	2.24	0.02	39.2	38.3	0.9
11	1.42	1.51	0.09	38.7	41.0	2.3
12	2.09	2.24	0.15	38.7	38.3	0.4
13	n/a	n/a	n/a	153.6	150.1	3.5
14	2.43, 2.02	2.43, 2.25	0.23	37.1	36.3	0.8
15	2.66	3.06	0.40	61.8	62.1	0.3
16	3.46	3.60	0.14	57.4	59.0	1.6
17	n/a	n/a	n/a	135.0	134.6	0.4
18	7.22	7.15	0.07	124.2	125.6	1.4
19	7.21	7.15	0.06	127.9	129.3	1.4
20	n/a	n/a	n/a	137.8	138.0	0.2
21	2.38	2.34	0.04	19.7	21.3	0.6
22	4.96, 4.90	4.89, 4.87	0.10	110.6	110.8	0.2
23	1.13	1.01	0.12	20.5	20.4	0.1
24	1.10	1.01	0.09	20.7	20.4	0.3
25	4.96, 4.93	4.89, 4.85	0.15	109.7	110.8	1.1
			Tot = 2.68 Avg = 0.14 std dev = 0.17			Tot = 26.4 Avg = 1.1 std dev = 1.5

*Computational experiments were conducted by Oliver Dutton

Table 35. Comparison of the predicted and synthetic ^{1}H and ^{13}C NMR shifts for **523a**

The DFT calculations were performed using Gaussian 09 at the B3LYP/6-31G(d)-IEFPCM($CHCl_3$) (geometry optimisation) and B3LYP/6-311G(d,p)-IEFPCM($CHCl_3$) (NMR calculation) level of theory.*



523a

Position	Predicted Data ^{1}H NMR ($CHCl_3$)	Synthetic Data ^{1}H NMR ($CDCl_3$)	Δδ (ppm)	Predicted Data ^{13}C NMR ($CHCl_3$)	Synthetic Data ^{13}C NMR ($CDCl_3$)	Δδ (ppm)
1	2.36	2.32	0.04	19.6	21.2	1.6
2	n/a	n/a	n/a	136.4	136.6	0.2
3	7.18	7.11	0.07	128.0	129.4	1.4
4	7.22	7.11	0.11	128.5	129.0	0.5
5	n/a	n/a	n/a	134.0	134.0	0
6	2.89, 2.53	2.92, 2.76	0.26	38.3	38.5	0.2
7	2.61	2.87	0.27	61.1	61.7	0.6
8	3.02	3.10	0.08	55.1	58.2	3.1
9	n/a	n/a	n/a	151.7	149.9	1.8
10	2.29	2.16	0.13	37.8	34.9	2.9
11	1.51	1.37	0.14	38.7	41.5	2.8
12	2.34	2.11	0.23	38.6	34.7	3.9
13	n/a	n/a	n/a	151.9	149.8	2.1
14	3.04	3.04	0	54.9	57.9	3.0
15	2.58	2.85	0.27	61.7	61.6	0.1
16	2.75, 2.61	2.92, 2.76	0.32	38.4	38.3	0.1
17	n/a	n/a	n/a	134.5	133.9	0.5
18	7.23	7.11	0.22	128.4	129.0	0.6
19	7.18	7.11	0.07	127.9	129.4	1.5
20	n/a	n/a	n/a	136.3	136.4	0.1
21	2.36	2.32	0.04	19.6	21.2	1.6
22	5.09, 4.95	4.98	0.14	111.3	109.4	1.9
23	0.93	0.98	0.05	19.1	21.0	0.9
24	0.97	0.87	0.12	19.0	20.4	1.4
25	5.05, 4.93	4.74	0.50	110.4	109.2	1.2
			Tot = 3.06 Avg = 0.16 std dev = 0.16			Tot = 34.0 Avg = 1.4 std dev = 1.8

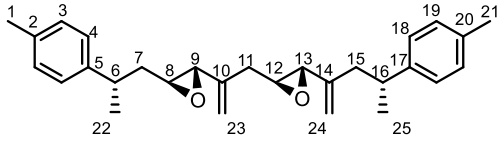
We were ready to predict the ^{1}H and ^{13}C NMR of **553**, but which of the eight diastereomers would we choose? We did not envisage being able to distinguish between the diastereomers using the computational method outlined above, however we did not wish to compute all of the diastereomers, as these calculations take a long time to perform. Most of all, we did not wish to discount the other seven diastereomers in the event that one diastereomer gave a negative result. With this in mind, we performed the prediction on diastereomers **553a** (Table 36) and **553b** (Table 37), as these were anticipated to produce NMR parameters that differed the most. In actual fact, the predicted ^{1}H and ^{13}C NMR shifts of diastereomers **553a** and **553b** were found to be quite similar. Upon comparison of the predicted chemical shifts with those reported for machillene, we were

*Computational experiments were conducted by Oliver Dutton

encouraged that **553** was indeed the correct structural isomer of the natural product. This was because the average errors in the NMR data for diastereomers **553a** (avg $\Delta\delta_H$ = 0.19 ppm, avg $\Delta\delta_C$ = 1.5 ppm) and **553b** (avg $\Delta\delta_H$ = 0.20 ppm, avg $\Delta\delta_C$ = 1.5 ppm) were only slightly higher than that of our control experiments using *anti*-**472** and **523a**.

Table 36. Comparison of the predicted ^{1}H and ^{13}C NMR shifts for **553a** with those reported for machillene.

The DFT calculations were performed using Gaussian 09 at the B3LYP/6-31G(d)-IEFPCM($CHCl_3$) (geometry optimisation) and B3LYP/6-311G(d,p)-IEFPCM($CHCl_3$) (NMR calculation) level of theory.* The synthetic data has been fitted to the reported data to give the best match.



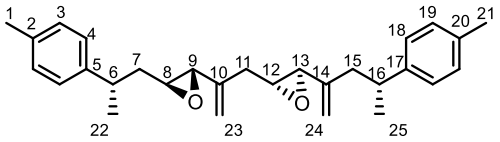
553a

Position	Reported Data ^{1}H NMR ($CDCl_3$)	Predicted Data ^{1}H NMR ($CDCl_3$)	$\Delta\delta$ (ppm)	Reported Data ^{13}C NMR ($CDCl_3$)	Predicted Data ^{13}C NMR ($CDCl_3$)	$\Delta\delta$ (ppm)
1	2.32	2.35	0.03	21.0	19.5	1.5
2	n/a	n/a	n/a	135.2	135.8	0.6
3	7.09	7.15	0.06	129.2	127.9	1.3
4	7.13	7.14	0.01	126.6	126.1	0.5
5	n/a	n/a	n/a	142.3	143.9	1.6
6	2.89	2.75	0.14	36.9	38.6	1.7
7	1.65, 1.65	1.85, 1.58	0.27	40.7	40.5	0.2
8	2.72	2.38	0.34	60.9	59.2	1.7
9	3.09	3.19	0.10	57.6	57.5	0.1
10	n/a	n/a	n/a	143.6	145.9	2.3
11	1.81, 1.81	2.32, 2.04	0.74	40.7	37.6	3.1
12	2.83	2.46	0.37	61.2	60.5	0.7
13	2.90	2.91	0.01	57.1	56.8	0.3
14	n/a	n/a	n/a	143.6	147.2	3.6
15	2.00, 2.00	2.33, 2.27	0.60	41.1	42.8	1.7
16	2.89	2.75	0.14	37.4	40.7	3.3
17	n/a	n/a	n/a	141.5	143.9	2.4
18	7.13	7.14	0.01	126.6	126.1	0.5
19	7.09	7.15	0.06	129.2	127.9	1.3
20	n/a	n/a	n/a	135.2	135.8	0.6
21	2.32	2.35	0.03	21.0	21.2	0.2
22	1.30	1.33	0.03	22.7	20.6	2.1
23	5.07, 4.95	5.20, 5.07	0.25	113.1	111.3	1.8
24	4.92, 4.85	5.19, 5.03	0.45	113.6	111.3	2.3
25	1.30	1.30	0.00	21.7	20.1	1.6
			Tot = 3.64			Tot = 37.0
			Avg = 0.19			Avg = 1.5
			std dev = 0.21			std dev = 1.9

*Computational experiments were conducted by Oliver Dutton

Table 37. Comparison of the predicted ^{1}H and ^{13}C NMR shifts for **553b** with those reported for machillene.

The DFT calculations were performed using Gaussian 09 at the B3LYP/6-31G(d)-IEFPCM($CHCl_3$) (geometry optimisation) or B3LYP/6-311G(d,p)-IEFPCM($CHCl_3$) (NMR calculation) level of theory.* The synthetic data has been fitted to the reported data to give the best match.



553b

Position	Reported Data ^{1}H NMR ($CDCl_3$)	Predicted Data ^{1}H NMR ($CDCl_3$)	Δδ (ppm)	Reported Data ^{13}C NMR ($CDCl_3$)	Predicted Data ^{13}C NMR ($CDCl_3$)	Δδ (ppm)
1	2.32	2.35	0.03	21.0	19.5	1.5
2	n/a	n/a	n/a	135.2	135.8	0.6
3	7.09	7.15	0.06	129.2	127.9	1.3
4	7.13	7.14	0.01	126.6	126.1	0.5
5	n/a	n/a	n/a	142.3	144.1	1.8
6	2.89	2.79	0.10	36.9	38.5	1.6
7	1.65, 1.65	1.81, 1.67	0.18	40.7	40.7	0
8	2.72	2.49	0.23	60.9	58.9	2.0
9	3.09	3.04	0.05	57.6	58.3	0.7
10	n/a	n/a	n/a	143.6	145.6	2.0
11	1.81, 1.81	2.29, 2.24	0.91	40.7	37.1	3.6
12	2.83	2.69	0.14	61.2	60.0	1.2
13	2.90	2.99	0.09	57.1	57.4	0.3
14	n/a	n/a	n/a	143.6	146.6	3.0
15	2.00, 2.00	2.29, 2.29	0.58	41.1	43.3	2.2
16	2.89	2.67	0.22	37.4	39.7	2.3
17	n/a	n/a	n/a	141.5	144.1	2.6
18	7.13	7.14	0.01	126.6	126.1	0.5
19	7.09	7.15	0.06	129.2	127.9	1.3
20	n/a	n/a	n/a	135.2	135.8	0.6
21	2.32	2.35	0.03	21.0	21.2	0.2
22	1.30	1.35	0.05	22.7	20.7	2.2
23	5.07, 4.95	5.28, 5.15	0.41	113.1	112.3	0.8
24	4.92, 4.85	5.22, 5.04	0.49	113.6	111.6	2.0
25	1.30	1.20	0.10	21.7	19.3	2.4
			Tot = 3.75 Avg = 0.20 std dev = 0.20			Tot = 37.2 Avg = 1.49 std dev = 1.88

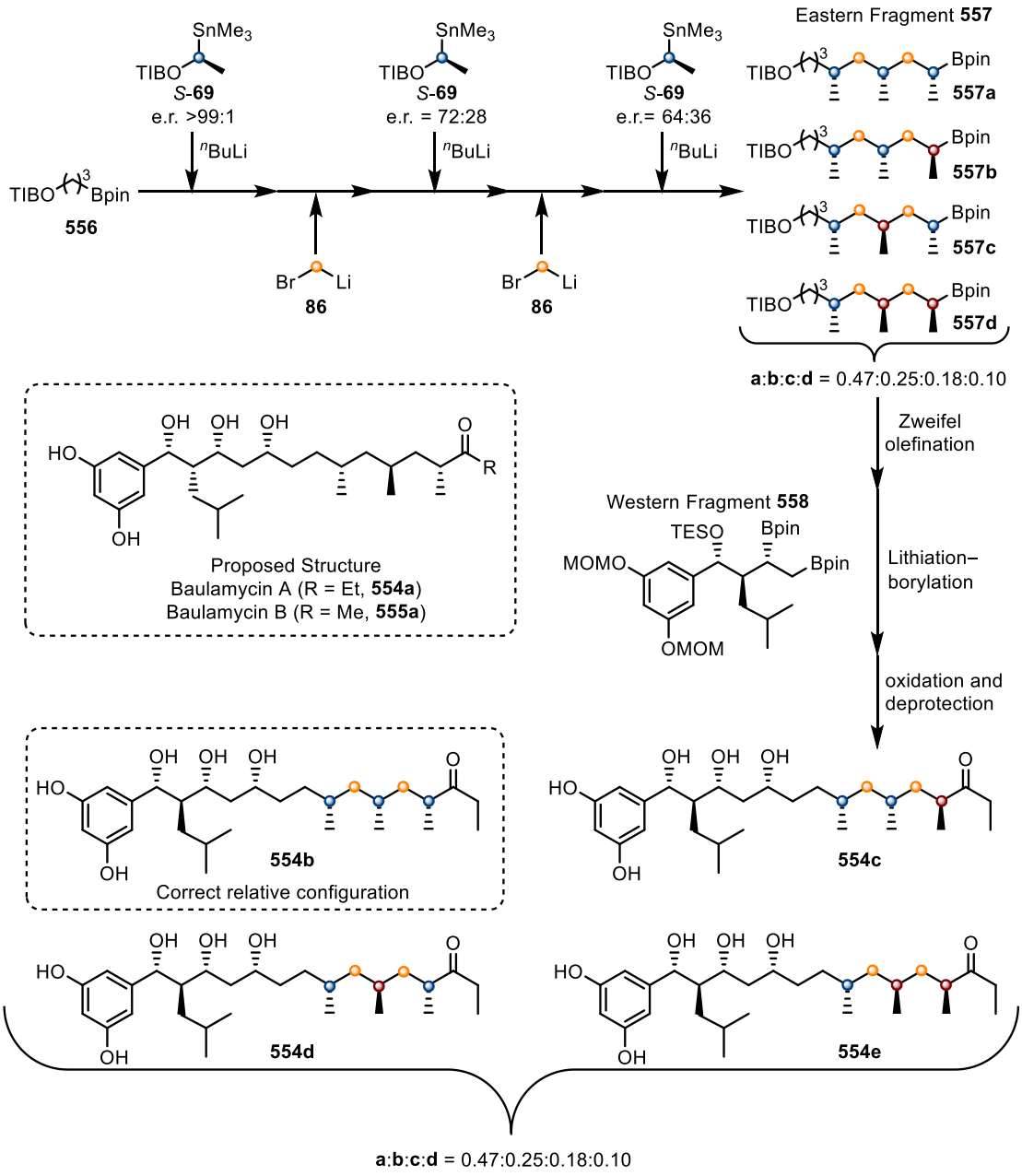
The next step of this project will be to determine the correct relative stereochemistry of **553** through synthesis (see section 4.4.), which will be conducted by another researcher.

*Computational experiments were conducted by Oliver Dutton

5.4. Conclusions & Outlook

In summary, we have developed a new procedure to achieve the vinylidene homologation of boronic esters. Computational studies have shown that, while both Peterson and boron-Wittig elimination pathways are feasible, the reaction outcome is governed by the ability to stabilise the negative charge that accumulates in the transition-state. This vinylidene homologation reaction was used to achieve a short and stereoselective synthesis of the proposed structure of machillene, which revealed that the isolation team had misassigned the structure of the natural product. Using the NMR prediction software iLab the structure was revised to **523a**, however, after conducting a synthesis, it was apparent that this revision was incorrect. Using a quantum mechanical approach, a second structural revision was performed. We are now confident that **553** is the correct structure of machillene, however we are still unsure of the correct relative stereochemistry. Therefore, future work will involve the preparation of all eight diastereomers of **553**, by use of a mixture-study approach.

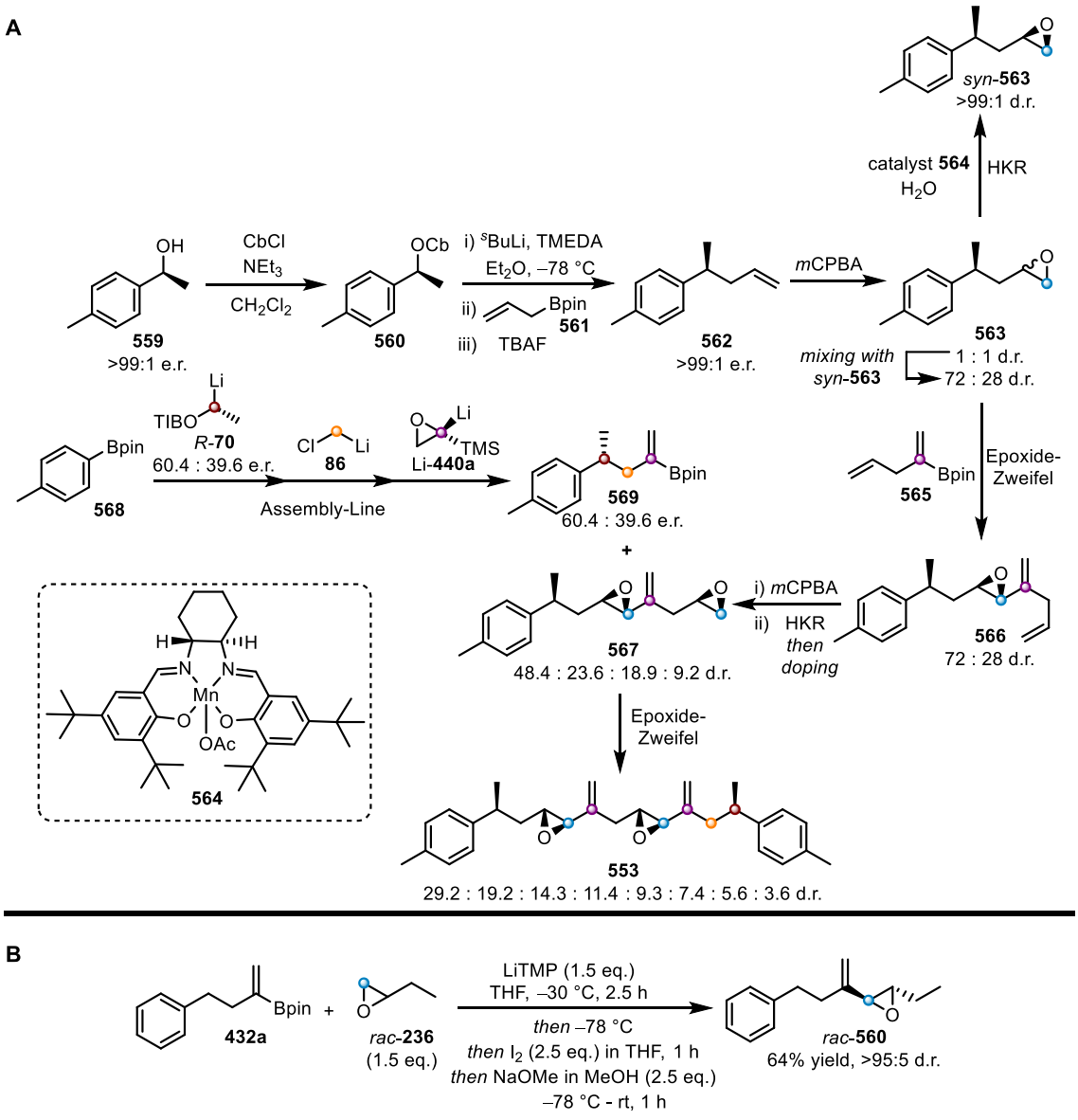
In 2017, Aggarwal and co-workers synthesised the reported structures of Baulamycin A (**554a**) and B (**555a**), however the experimental and reported data did not match (Scheme 114).[194] Using computational analysis and comparisons with literature databases, the authors were able to identify the correct relative stereochemistry of Western fragment **558** of the natural product. However, for Eastern fragment **557**, the diastereomers could not be distinguished between by computation. Therefore, by exploiting the exquisite reagent control provided by assembly–line synthesis, the authors generated an encoded mixture of all four diastereomers of **557**, the ratio of which was governed by the enantiopurity of α-stannyl benzoate **69**. Precise enantiomeric mixtures of **69** were obtained by doping of an enantiopure sample of *S*-**69** with varying quantities of the opposite enantiomer, *R*-**69**. The enantiomeric ratios of **69** were selected such that each ratio of fragment **557** could be accurately quantified by ^{13}C NMR and so that the peak intensities were maximally distributed. After joining the encoded mixture of Eastern fragment **557** to Western fragment **558** *via* a lithiation–borylation reaction, the ^{13}C NMR chemical shifts of the encoded diastereomeric mixture of **554b-e** was compared with the isolation data, which revealed the correct relative configuration of the Baulamycins. This structural elucidation strategy was termed a “mixture-study approach”.



Scheme 114. Mixture-study approach reveals the correct relative configuration of the Baulamycins

In order to perform a mixture study approach towards **553**, we must design a synthesis whereby the configuration of all of the stereocentres can be reliably controlled (Scheme 115A). The synthesis will begin with preparation of carbamate **560** from benzylic alcohol **559**, which is commercially available in enantiopure form. We envisage that carbamate **560** will undergo a lithiation–borylation/protodeboronation[195] sequence to provide terminal alkene **562** as a single enantiomer, which will subsequently be treated with *m*CPBA to deliver epoxide **563** as a 1:1 mixture of diastereomers. It is expected that

subjection of this diastereomeric mixture to Jacobsen's hydrolytic kinetic resolution (HKR)[103] will deliver *syn*-**563** as a single diastereomer (>99:1 d.r.). Doping the 1:1 diastereomeric mixture of **563** with a specific quantity of *syn*-**563** will allow tuning of the diastereomeric ratio to the desired value (72:28 d.r.). Subjection of the 72:28 diastereomeric mixture of **563** to an epoxide-Zweifel reaction with vinyl boronic ester **565** will provide *trans*-vinyl epoxide **566** (72:28 d.r.). Preliminary studies have demonstrated that this reaction is indeed feasible (Scheme 115B). A second sequence of epoxidation, kinetic resolution and doping should deliver bis-epoxide **567** in a diastereomeric ratio of 48.4:23.6:18.8:9.2. Next, a second epoxide-Zweifel reaction between **567** and vinyl boronic ester **569** (60.4:39.6 d.r.), which will be prepared from boronic ester **568** using assembly-line synthesis, will give final product **553** as a precise mixture of eight diastereomers (29.2:19.2:14.3:11.4:9.3:7.4:5.6:3.6 d.r.). Finally, using quantitative ^{13}C NMR analysis, the chemical shifts of the synthetic mixture will be compared to the reported data in order to distinguish the relative stereochemistry of machillene. If successful, this approach will allow the structural revision of machillene and validate our computational hypothesis.



Scheme 115. A) Proposed mixture-study approach towards **553**

B) Preliminary result for the epoxide-Zweifel reaction

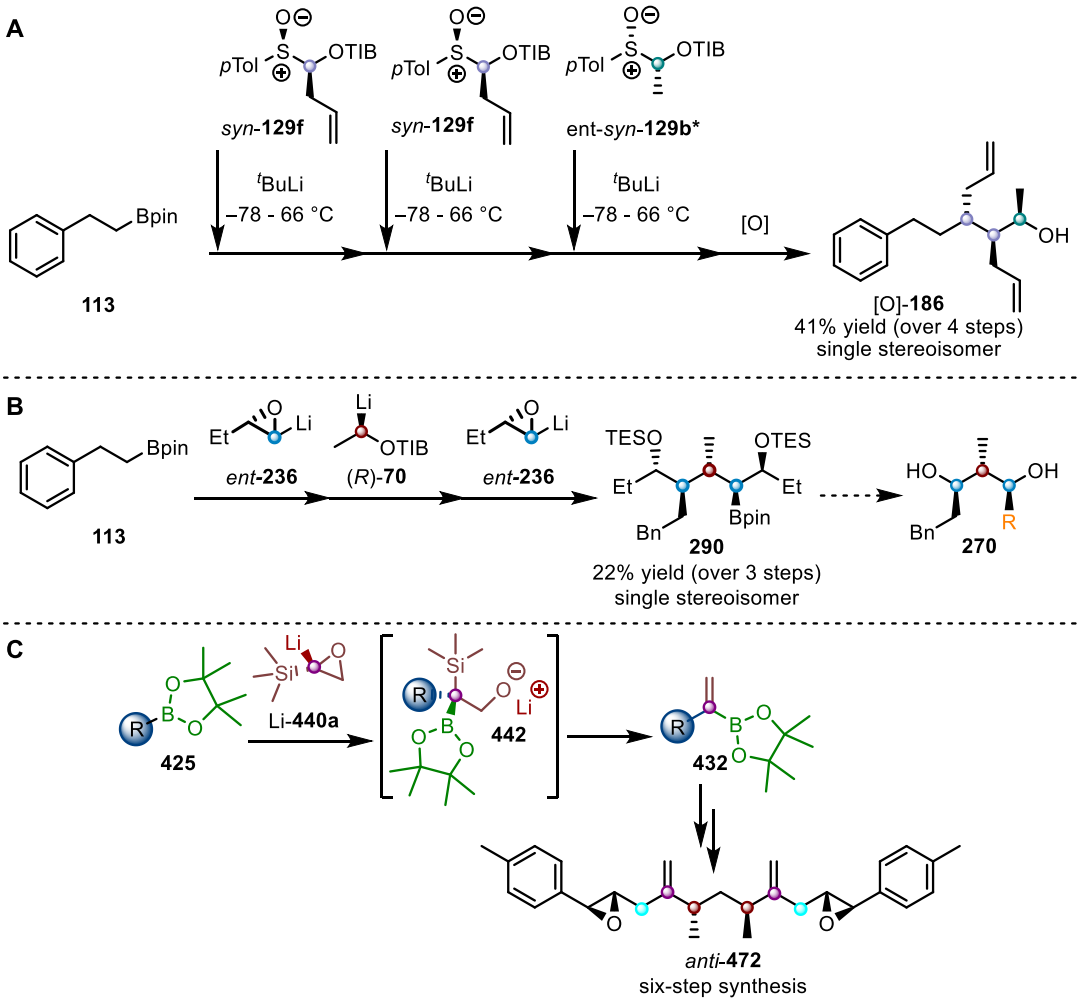
6. General Conclusion

The homologation of boronic esters is a useful strategy for accessing functionalised and stereodefined boronic esters, which can then be further utilised.

For example, the iterative homologation of boronic esters with carbenoids derived from enantioenriched α-sulfinyl benzoates has been shown to deliver a molecule bearing three contiguous stereocentres as a single stereoisomer (Scheme 116A). We envisage that the α-sulfinyl benzoate building-blocks, which have greatly expanded the range of accessible stereopure carbenoids, will be of use to the wider scientific community. Indeed, these carbenoid precursors are currently being utilised by our group in a number of total syntheses.

When rendered iterative, the homologation of boronic esters can be used to access challenging structural motifs. For example, by alternating between lithiated α-chlorosilane and lithiated TIB ester building blocks, the stereocontrolled synthesis of polypropionate motifs was achieved.[49] Due to a number of drawbacks, namely poor step-efficiency, an alternative iterative strategy, which utilised enantioenriched lithiated epoxide Li-**236** as the carbenoid, was explored for the synthesis of polypropionate fragments (Scheme 116B). However, this method was found to be less efficient than the lithiated α-chlorosilane protocol and was abandoned. New avenues towards polypropionate fragments are currently under investigation by our group, one of which utilises α-sulfinyl benzoate building blocks.

Due to the vast range of accessible carbenoids and boronic esters, homologation reactions allow access to a plethora of sp^3-rich molecules. For example, the vinylidene homologation gave access to pharmaceutically relevant cyclobutyl and azetidinyl vinyl boronic esters **432f** and **432g**, which would be difficult to prepare by other means. The iterative homologation of boronic esters has been a valuable strategy for the synthesis of complex molecules and we hope that these reactions will continue to play a pivotal role in future total syntheses, not least in the preparation of **553** (Scheme 116C).



Scheme 116. General overview of research

7. Experimental

7.1. General Information

All air- and water-sensitive reactions were carried out in oven-dried or flame-dried glassware under a N_2 atmosphere using standard Schlenk techniques. Analytical TLC was performed on aluminium-backed plates pre-coated (0.25 mm) with Merck Silica Gel 60 F254. Compounds were visualized by exposure to UV-light or stained using $KMnO_4$, *p*-anisaldehyde or phosphomolybdic acid (PMA) followed by heating. Flash column chromatography was performed using Sigma Aldrich silica gel 60 (40-63 μm) or basic silica gel (see Materials & Reagents). All mixed solvent eluents are reported as v/v solutions.

^{1}H- and ^{13}C- NMR spectra were acquired at various field strengths as indicated using JEOL ECS 300, JEOL ECS 400, Varian 400, Varian VNMRS500, Bruker 400 and Bruker Cryo 500 MHz spectrometers. ^{1}H and ^{13}C NMR spectra were referenced internally to the residual non-deuterated solvent signal. ^{1}H and ^{13}C NMR coupling constants are reported in Hertz (Hz). Coupling constants are reported as follows: s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, pent = pentet, sext = sextet, sept = septet, m = multiplet, dd = doublet of doublet, etc. Assignment of signals in ^{1}H- and ^{13}C-spectra was performed using ^{1}H-^{1}H COSY, DEPT, HSQC and HMBC experiments where appropriate. ^{13}C signals adjacent to boron are generally not observed due to quadrupolar relaxation.

High resolution mass spectra were recorded on Bruker Daltonics MicroTOF II by using Electronic Ionization (EI), Electrospray Ionization (ESI), Matrix Assisted Laser Desorption Ionization (MALDI) and Atmospheric Pressure Chemical Ionisation (APCI). GC-MS was performed on an Agilent 6890 apparatus. All IR data was obtained on a Perkin-Elmer Spectrum One FT-IR spectrometer. Optical rotations were obtained on a Bellingham and Stanley Ltd. ADP220 polarimeter. Melting point ranges were determined using a Stuart SMP30 advanced digital melting point apparatus and are reported uncorrected. Chiral HPLC was performed using Daicel Chiralpak IA, IB and IC columns (4.6 mm× 250 mm, 5 μm) fitted with the respective guard (4 mm ×10 mm) and monitored by DAD (Diode Array Detector) on an Agilent 1100 system equipped with HP Chemstation/OpenLab software.

7.2. Materials & Reagents

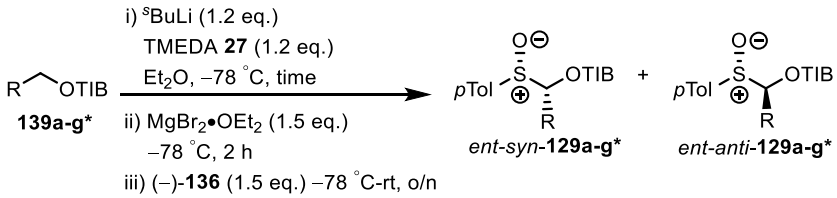
All reagents were used as received unless otherwise stated. Anhydrous Et_2O, THF, and CH_2Cl_2 were dried using a purification column composed of activated alumina and stored over 3 Å mol sieves. For the lithiation of epoxysilane **440a**, HPLC grade pentane (Sigma Aldrich) was stored over activated 3 Å molecular sieves for 2 days prior to use. TMEDA **27** and 2,2,6,6-tetramethylpiperidine were distilled over CaH_2 and stored in a Young's tube under N_2. Diisopropylamine was dried over NaOH before distillation and stored in a Young's tube under N_2. Organolithium reagents (^{n}BuLi, ^{s}BuLi, and ^{t}BuLi) were periodically titrated using *N*-benzylbenzamide.[196] ^{i}PrMgCl•LiCl was titrated using I_2.[197] LDA, LiTMP and lithium LiHMDS solutions were freshly prepared from the corresponding distilled amines and ^{n}BuLi immediately before use. Basic silica gel was prepared by adding trimethylamine (2 mL) to a slurry of SiO_2 (~100 g) in Et_2O and allowing the solvent to evaporate overnight.

Sulfinates **136** and *ent*-**136**, benzyl bromide, 4-bromobenzyl bromide, 3-bromo-1-(trimethylsilyl)-1-propyne, TMPMgCl•LiCl, 2-ethyl oxirane *rac*-**236**, (*S*)-2-ethyl oxirane *ent*-**236**, vinyltrimethylsilane (**458a**), vinyl silane **458d**, 2-(but-3-en-1-yl)oxirane (**463**), 4-methylpent-1-ene, diboron **404a**, PEPPSI-IPr catalyst, $Pd(OAc)_2$ and DavePhos were purchased from Sigma Aldrich. Cyclohexyl boronic ester **121**, 2,4,6-triisopropylbenzoic acid, *p*-tolyl methyl sulfide, chlorosilane **468** and Pd(DPEPhos)Cl_2 were purchased from Alfa Aesar. *p*-Trifluoromethylphenyl boronic ester **425q** was purchased from Santa Cruz Biotechnology. Phenethyl boronic acid was purchased from Fluorochem Ltd.

7.3. α-Sulfinyl Benzoates as Carbenoid Precursors for the Homologation of Boronic Esters

7.3.1. *General Procedures*

General procedure 1 (GP1): Synthesis of *syn*- and *anti*- α-sulfinyl benzoates by transmetallation

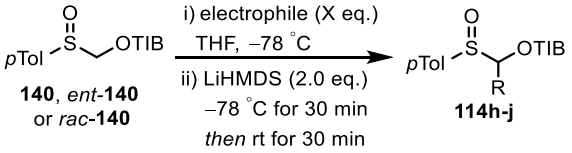


To a stirred solution of 2,4,6-triisopropylbenzoate **139** (1.0 eq.) and TMEDA **27** (1.2-1.5 eq.) in anhydrous Et_2O (0.3 M) was added ^sBuLi (1.3 M in cyclohexane/hexane, 1.2-1.5 eq.) dropwise (1 mL/min) at –78 °C. After stirring for the required time at –78 °C a solution of freshly prepared $MgBr_2•Et_2O$* (1.5 eq. in Et_2O - 0.8 M) was added dropwise at –78 °C and the reaction mixture was stirred for 2 h at this temperature. At this point a solution of (1*R*,2*S*,5*R*)-(–)-menthyl (*S*)-*p*-toluenesulfinate (**136**) (1.5 eq.) or *ent*-**136** in anhydrous THF (1.0 M) was added dropwise at –78 °C. The mixture was stirred for an additional 1 h before being warmed to room temperature and stirred overnight. The reaction mixture was then diluted with EtOAc and sat. $NH_4Cl_{(aq)}$, the phases were separated and the aqueous phase was extracted with EtOAc (×3). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. In many cases separation of the desired diastereomers from the menthol by-product was facilitated by silylation of menthol; to a solution of the crude mixture in anhydrous CH_2Cl_2 (0.5 M) was added Et_3N (1.5 eq.). TMSCl (1.3 eq.) was added dropwise at room temperature, the resulting mixture was stirred for 20 min, diluted with Et_2O and washed with H_2O. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give a crude residue, which was purified by flash column chromatography to afford the *syn* (less polar) and the *anti* (more polar) diastereomers.

* A solution of $MgBr_2•Et_2O$ was prepared as follows: Mg turnings (4.0 eq.) were added to a Schlenk tube under a N_2 atmosphere and anhydrous Et_2O (0.8 M with respect to

dibromoethane) was added. Dibromoethane (1.5 eq.) was added dropwise and a reflux was maintained until addition had finished. After gas evolution ceased, the reaction mixture was stirred for an additional 30 min.

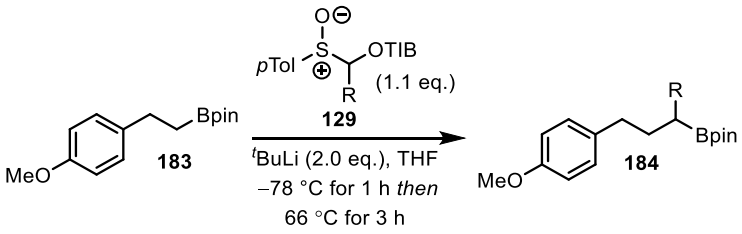
General procedure 2 (GP2): Synthesis of *syn*- and *anti*- α-sulfinyl benzoates by alkylation



((*S*)-*p*-Tolylsulfinyl)methyl-2,4,6-triisopropylbenzoate (**140**) or *ent*-**140** (1.0 eq.) and alkylating/fluorinating agent (1.1-2.0 eq.) in an oven dried Schlenk tube was dissolved in anhydrous THF (0.2 M) under an atmosphere of nitrogen. The reaction mixture was cooled to –78 °C and base (2.0 eq.) was added dropwise (0.5 mL/min). The mixture was stirred at –78 °C for 30 min and then the cooling bath was removed and the solution was stirred at room temperature for 30 min. The reaction mixture was quenched with sat. NH_4Cl and diluted with EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc (×3). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography to give the *syn* (less polar) and the *anti* (more polar) diastereomers.

The racemates were synthesised as above but using racemic sulfoxide *rac*-**140** as the starting material.

General procedure 3 (GP3): Stereocontrolled homologation of boronic esters using α-sulfinyl benzoates: *in-situ* procedure using ^{t}BuLi



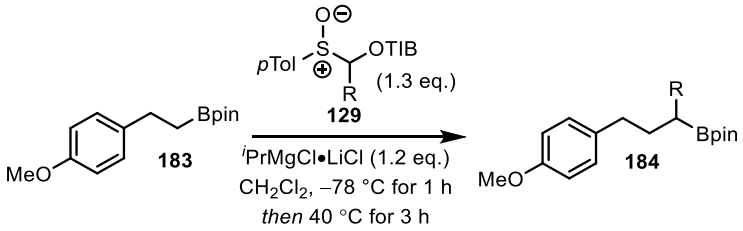
^{t}BuLi (1.7 M in pentane, 2.00 eq.) was added dropwise (0.2 mL/min) to a mixture of α-sulfinyl benzoate **129** (1.05-1.10 eq.) and pinacol boronic ester **183** (1.00 eq.) in anhydrous THF (0.1 M with respect to the boronic ester) at –78 °C and the resulting solution was stirred at this temperature for 1 h. After warming to room temperature, the reaction mixture was heated at 66 °C for 3 h, cooled to room temperature, diluted with Et_2O and sat. $NH_4Cl_{(aq)}$ was added. The phases were separated and the aqueous phase was

extracted with Et_2O (×3). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure (where specified the work-up procedure was modified and the crude reaction mixture was filtered through basic silica (see materials and reagents)(~10 mm depth of wetted (Et_2O) silica) and the solvent was removed under reduced pressure). Purification of the crude reaction mixture by flash column chromatography afforded the desired homologated boronic ester **184**. A small portion of the boronic ester was oxidised to the corresponding alcohol [O]-**184** following **GP5** to determine the stereospecificity of the reaction.

When the separation of the homologated boronic ester **184** from the unreacted starting boronic ester **183** was not possible the mixture was oxidised (see **GP5**) and the corresponding alcohol [O]-**184** was isolated.

The racemates were synthesised as above but using the corresponding racemic sulfoxides as starting material.

General procedure 4 (GP4): Stereocontrolled homologation of boronic esters using α-sulfinyl benzoates: *in-situ* procedure using ^{i}PrMgCl•LiCl

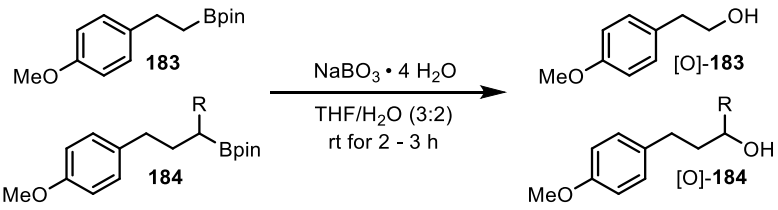


^{i}PrMgCl•LiCl (1.3 M in THF, 1.2 eq.) was added dropwise (0.2 mL/min) to a mixture of α-sulfinyl benzoate **129** (1.3 eq.) and pinacol boronic ester **183** (1.0 eq.) in anhydrous CH_2Cl_2 (0.1 M with respect to the boronic ester) at –78 °C and the resulting solution was stirred at this temperature for 1 h. After warming to room temperature, the reaction mixture was heated at 40 °C for 3 h, cooled to room temperature, diluted with Et_2O and sat. $NH_4Cl_{(aq)}$ was added. The phases were separated and the aqueous phase was extracted with Et_2O (×3). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure (where specified the work-up procedure was modified and the crude reaction mixture was filtered through basic silica (see materials and reagents)(~10 mm depth of wetted (Et_2O) silica) and the solvent was removed under reduced pressure).The crude mixture was purified by flash column chromatography to afford the desired homologated boronic ester **184**.

When the separation of the homologated boronic ester **184** from the unreacted starting boronic ester **183** was not possible the mixture was oxidised (see **GP5**) and the corresponding alcohol [O]-**184** was isolated.

The racemates were synthesised as above but using the corresponding racemic sulfoxides as the starting materials.

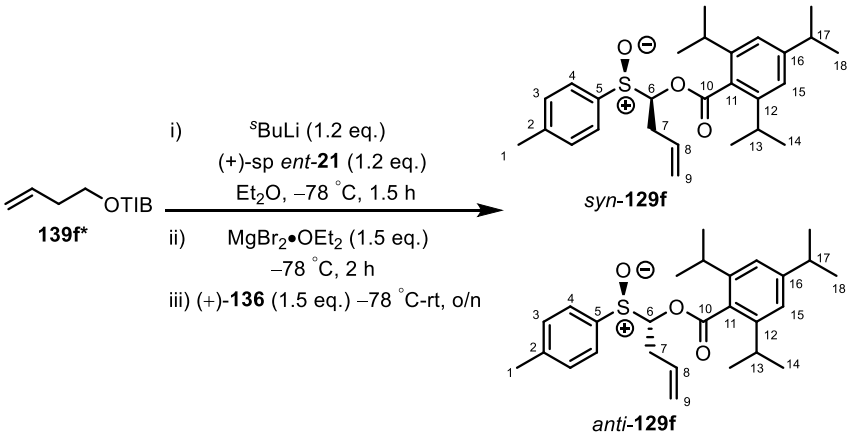
General procedure 5 (GP5): Stereospecific oxidation of boronic esters using sodium perborate tetrahydrate



To a solution of boronic ester mixture (0.2-0.3 mmol) in THF/water (3:2, 0.1 M) at room temperature was added $NaBO_3 \bullet 4H_2O$ (10 eq.) and the resulting suspension was stirred for 2-3 h. The mixture was filtered through silica [~10 mm depth of wetted (Et_2O) silica] and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography to afford the desired alcohol [O]-**184**.

7.3.2. *Preparation of Individual Compounds*

(*R*)-1-((*R*)-*p*-tolylsulfinyl)but-3-en-1-yl 2,4,6-triisopropylbenzoate *syn*-(**129f**) **and (*S*)-1-((*R*)-*p*-tolylsulfinyl)but-3-en-1-yl 2,4,6-triisopropylbenzoate** *anti*-(**129f**)



Following modified **GP1**, homoallylic benzoate **139f*** (7.56 g, 25.0 mmol), (+)-sparteine *ent*-(**21**) (6.91 mL, 30.0 mmol), ^{s}BuLi (1.35 M in cyclohexane/hexane, 23.1 mL, 30.0 mmol – lithiation time = 1.5 h), Mg turnings (2.40 g, 100.0 mmol), dibromoethane (3.35 mL, 37.5 mmol), (1*S*,2*R*,5*S*)-(+)-menthyl (*S*)-*p*-toluenesulfinate *ent*-(**136**) (11.1 g, 37.5 mmol), Et_3N (5.23 mL, 50.0 mmol) and TMSCl (4.16 mL, 32.5 mmol). Purification of the crude residue (93:7 d.r.) by flash column chromatography (Hexane:EtOAc = 100:0 → 90:10) gave *syn*-**129f** (less polar, 9.83 g, 70%) as a white solid and *anti*-**129f** (more polar, 930 mg, 8%, 10:1 d.r.) as a dense colourless oil.

syn-**129f**

$[\alpha]^{22}_{D}$: – 158 ° (*c* 0.3, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.67 (d, *J* = 8.0 Hz, 2H, H-4), 7.38 (d, *J* = 8.0 Hz, 2H, H-3), 7.04 (s, 2H, H-15), 5.75 (dd, J_1 = 10.0 Hz, J_2 = 3.0 Hz, 1H, H-6), 5.67 (m, 1H, H-8), 5.11–5.06 (m, 2H, H-9), 2.91 (sept, *J* = 6.6 Hz, 3H, H-13 and H-17), 2.72 (m, 1H, H-7a), 2.44 (s, 3H, H-1), 2.42 (m, 1H, H-7b), 1.28–1.23 (m, 18H, H-14 and H-18) ppm

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 170.1 (CO), 150.7 (C), 145.1 (2 × C), 141.6 (C), 137.2 (C), 131.3 (CH), 130.0 (2 × CH), 128.7 (C), 124.3 (2 × CH), 120.9 (2 × CH), 119.2 (CH_2), 91.3 (CH), 34.3 (CH), 31.4 (2 × CH), 27.7 (CH_2), 24.3 (2 × CH_3), 24.1 (2 × CH_3), 23.8 (2 × CH_3), 21.3 (CH_3) ppm

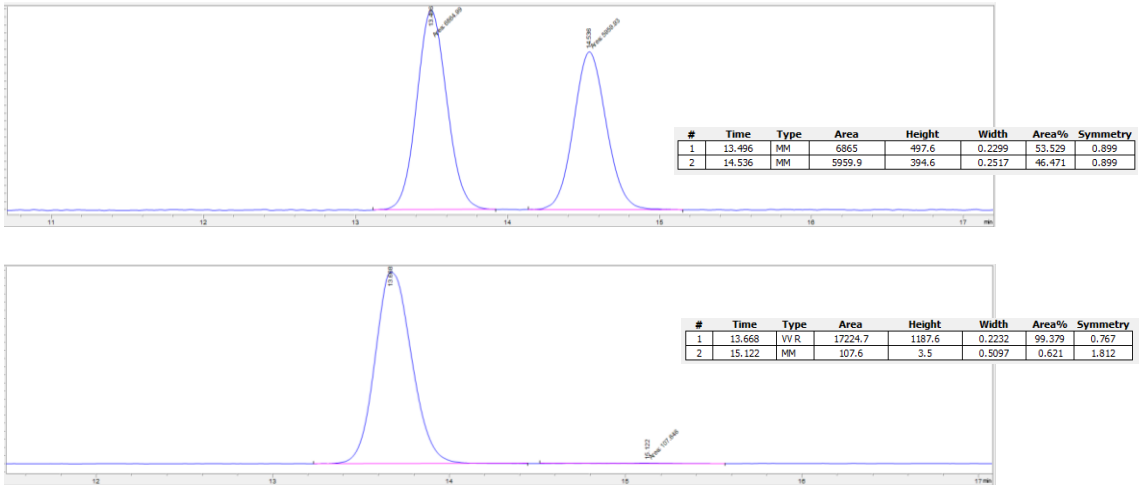
IR (neat): 2961, 1740, 1230, 1056, 1038, 877, 809 cm^{-1}

HRMS (ESI) calculated for $C_{27}H_{36}NaO_3S$: 463.2277, found: 463.2276

M.P. 85–87 ºC (EtOAc)

R_f: 0.17 (Pentane:EtOAc = 90:10)

Chiral HPLC: (Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm): tR = 13.5 minutes (maj), 14.5 minutes (min), e.r. > 99:1



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.496	MM	6865	497.6	0.2299	53.529	0.899
2	14.536	MM	5959.9	394.6	0.2517	46.471	0.899

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.668	VV R	17224.7	1187.6	0.2232	99.379	0.767
2	15.122	MM	107.6	3.5	0.5097	0.621	1.812

anti-**129f**

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.55 (d, *J* = 8.1 Hz, 2H, H-4), 7.32 (d, *J* = 8.1 Hz, 2H, H-3), 7.02 (s, 2H, H-15), 6.07 (dd, J_1 = 8.9 Hz, J_2 = 3.6 Hz, 1H, H-6), 5.78 (m, 1H, H-8), 5.15 (m, 2H, H-9), 2.90 (sept, *J* = 7.0 Hz, 1H, H-17), 2.83 (sept, *J* = 6.7 Hz, 2H, H-13), 2.70 (m, 1H, H-7a), 2.42 (s, 3H, H-1), 2.08 (m, 1H, H-7b), 1.26–1.18 (m, 18H, H-14 and H-18) ppm

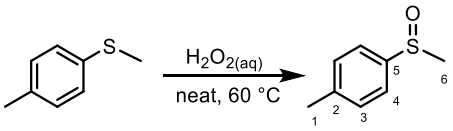
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 169.1 (CO), 150.6 (C), 145.2 (2 × C), 142.1 (C), 136.0 (C), 131.3 (CH), 129.8 (2 × CH), 128.8 (C), 125.4 (2 × CH), 120.9 (2 × CH), 119.5 (CH_2), 87.2 (CH), 34.3 (CH), 31.8 (CH_2), 31.3 (2 × CH), 24.4 (2 × CH_3), 24.0 (2 × CH_3), 23.8 (2 × CH_3), 21.4 (CH_3) ppm

IR (neat): 2961, 1740, 1230, 1056, 1038, 877, 809 cm^{-1}

HRMS (ESI) calculated for $C_{27}H_{36}NaO_3S$: 463.2277, found: 463.2276

R_f: 0.15 (Pentane:EtOAc = 90:10)

1-Methyl-4-(methylsulfinyl)benzene *rac*-(**142**)



rac-**142**

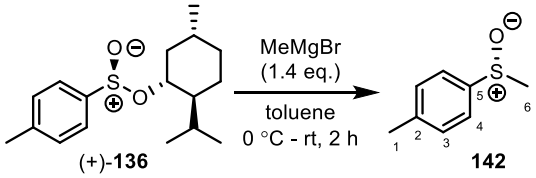
A mixture of *p*-tolylmethyl sulfide (1.35 mL, 10.0 mmol) and H_2O_2 (30%, 1.08 mL, 11.0 mmol) was heated at 60 °C for 16 h. The reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (5 mL) and water (5 mL). The phases were separated and the organic phase was washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc) to afford *rac*-**142** (1.41 g, 92%) as a colourless oil, which crystallised into a white solid on standing.

^{1}H NMR (CDCl3, 400 MHz) δ: 7.53 (d, *J* = 8.4 Hz, 2H, H-4), 7.32 (d, *J* = 8.4 Hz, 2H, H-3), 2.70 (s, 3H, H-6), 2.41 (s, 3H, H-1) ppm

^{13}C NMR (CDCl3, 101 MHz) δ: 142.6 (C), 141.6 (C), 130.1 (2 × CH), 123.6 (2 × CH), 44.1 (CH_3), 21.5 (CH_3) ppm

Data in accordance with that reported in the literature.[198]

(*R*)-1-Methyl-4-(methylsulfinyl)benzene (142)

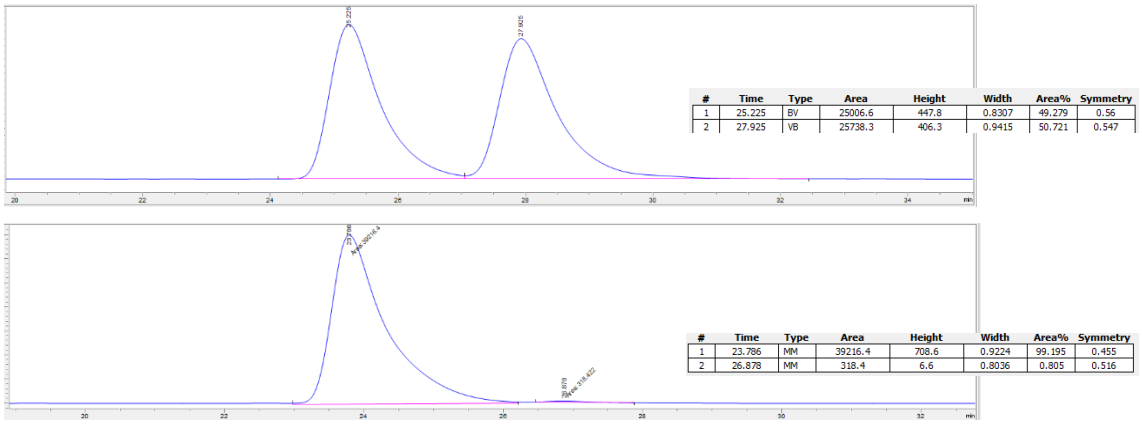


Prepared according to Yamakawa *et al.* [71]

[α]$^{22}_{D}$: + 148 ° (*c* 1.0, acetone), **[α]$^{22}_{D}$$^{lit.}$**: + 150.4 ° (*c* 1.17, acetone)[71]

Data in accordance with that described above.

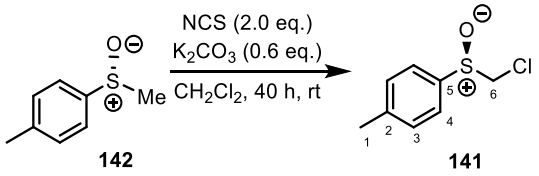
Chiral HPLC: (Daicel Chiralcel-OD-H column (25 cm), hexane:isopropanol = 92:8, 0.5 mL/min, room temperature, 210.8 nm): tR = 25.2 minutes (maj), 27.9 minutes (min), e.r. >99:1



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	25.225	BV	25006.6	447.8	0.8307	49.279	0.56
2	27.925	VB	25738.3	406.3	0.9415	50.721	0.547

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	23.786	MM	39216.4	708.6	0.9224	99.195	0.455
2	26.878	MM	318.4	6.6	0.8036	0.805	0.516

(*R*)-1-((chloromethyl)sulfinyl)-4-methylbenzene (141)



Prepared according to Yamakawa *et al.*[71]

[α]$^{22}_{D}$: – 195 ° (*c* 1.0, acetone), **[α]$^{22}_{D}$$^{lit.}$**: – 239.0 ° (*c* 1.17, acetone, (*R*))[71]

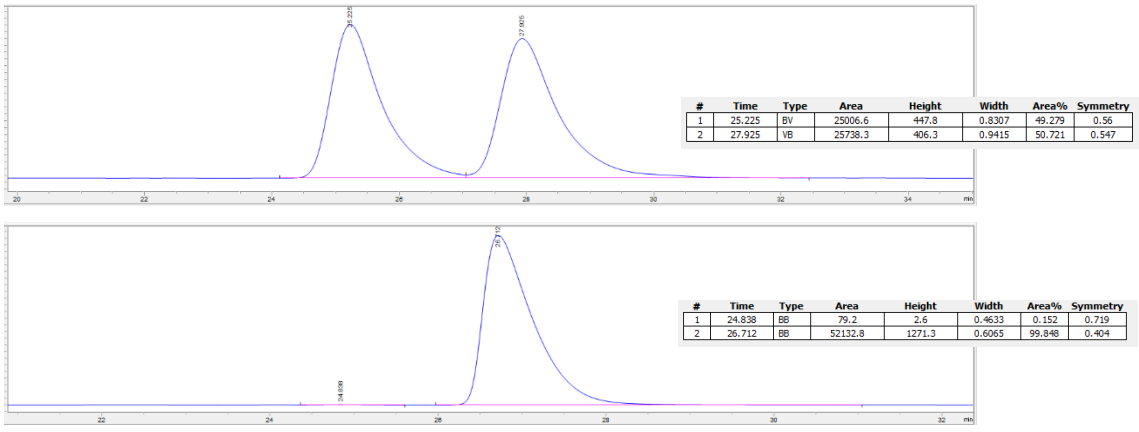
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.59 (d, *J* = 8.2 Hz, 2H, H-4), 7.36 (d, *J* = 8.2 Hz, 2H, H-3), 4.36 (s, 2H, H-6), 2.44 (s, 3H, H-1) ppm

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 142.9 (C), 137.7 (C), 130.0 (2 × CH), 124.8 (2 × CH), 61.2 (CH_2), 21.5 (CH_3) ppm

Data in accordance with that reported in the literature.[71]

rac-**141** was prepared using the same procedure but with *rac*-**142**.

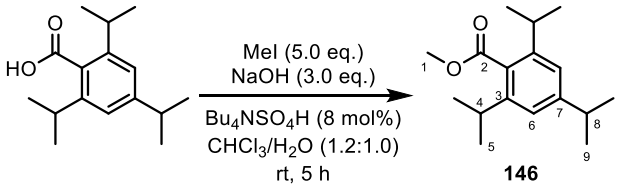
Chiral HPLC: (Daicel Chiralcel-IB column (25 cm), hexane:isopropanol = 90:10, 0.5 mL/min, room temperature, 210.8 nm): tR = 25.2 minutes (min), 27.9 minutes (maj), e.r. >99:1



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	25.225	BV	25006.6	447.8	0.8307	49.279	0.56
2	27.925	VB	25738.3	406.3	0.9415	50.721	0.547

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	24.838	BB	79.2	2.6	0.4633	0.152	0.719
2	26.712	BB	52132.8	1271.3	0.6065	99.848	0.404

Methyl 2,4,6-triisopropylbenzoate (**146**)



A biphasic mixture of 2,4,6-triisopropylbenzoic acid (7.44 g, 30.0 mmol), tetrabutylammonium hydrogen sulfate (816 mg, 2.40 mmol), sodium hydroxide (3.60 g, 90.2 mmol) and methyl iodide (9.35 mL, 150 mmol) in chloroform:water (1.22:1, v/v, 282 mL) was stirred vigorously for 5 h at room temperature. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give **146** as a crude pink solid (7.43 g, 95%), which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (s, 2H, H-6), 3.89 (s, 3H, H-1), 2.89 (sept, *J* = 7.4 Hz, 1H, H-8), 2.82 (sept, *J* = 7.4 Hz, 2H, H-4), 1.25 (d, *J* = 7.4 Hz, 18H, H-5 and H-9) ppm

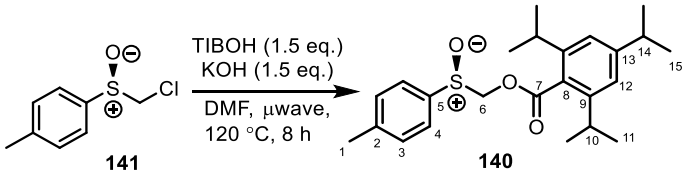
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.9 (CO), 150.2 (C), 144.8 (2 × C), 130.8 (C), 120.9 (2 × CH), 60.8 (CH_3), 34.6 (CH), 31.5 (2 × CH), 24.2 (4 × CH_3), 24.0 (2 × CH_3) ppm

IR (neat): 2957, 2869, 1719, 1254, 1080, 809 cm^{-1}

HRMS (ESI): calculated for $C_{17}H_{26}O_2Na$: 285.1825, found 285.1837

M.P. 40–42 ºC (CH_2Cl_2)

(*R*)-(*p*-Tolylsulfinyl)methyl 2,4,6-triisopropylbenzoate (**140**)



KOH (269 mg, 4.79 mmol) was added to a solution of 2,4,6-triisopropylbenzoic acid (1.19 g, 4.79 mmol) in dry DMF (5.4 mL) at room temperature and the resulting mixture was stirred for 30 min. (–)-(*R*)-chloromethyl *p*-tolyl sulfoxide (**142**) (600 mg, 3.19 mmol) was added and the reaction mixture was heated at 150 °C under μwave irradiation for 8 h. The solution was then allowed to cool to room temperature and was diluted with sat. $NH_4Cl_{(aq)}$ (10 mL) and EtOAc (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with water (3 x 30 mL), with NaOH (1.0 M, 2 x 30 mL), washed with brine (3 x 30 mL), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (Pentane:EtOAc = 75:25) to afford sulfoxide **140** (1.15 g, 90%) as a viscous colourless oil, which crystallised into a white solid upon standing.

$[\alpha]^{22}_D$: – 131 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.2 Hz, 2H, H-4), 7.37 (d, *J* = 8.2 Hz, 2H, H-3), 7.02 (s, 2H, H-12), 5.28 (d, *J* = 10.4 Hz, 1H, H-6a), 5.00 (d, *J* = 10.4 Hz, 1H, H-6b), 2.90 (sept, *J* = 7.0 Hz, 1H, H-14), 2.84 (sept, *J* = 6.8 Hz, 2H, H-10), 2.44 (s, 3H, H-1), 1.25 (d, *J* = 7.0 Hz, 12H, H-15), 1.23 (d, *J* = 6.8 Hz, 6H, H-11) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 169.8 (CO), 151.1 (C), 145.4 (2 × C), 142.5 (C), 137.4 (C), 130.3 (2 × CH), 128.6 (C), 124.8 (2 × CH), 121.1 (2 × CH), 83.4 (CH_2), 34.6 (CH), 31.8 (2 × CH), 24.4 (2 × CH_3), 24.3 (2 × CH_3), 24.1 (2 × CH_3), 21.6 (CH_3) ppm

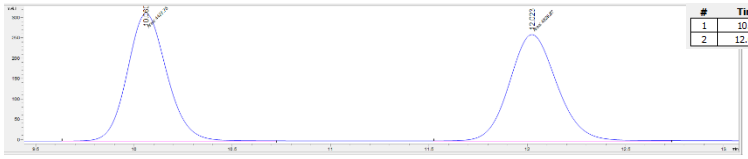
IR (neat): 2961, 1745, 1227, 1035, 816 cm^{-1}

HRMS (ESI) calculated for $C_{24}H_{32}O_3SNa$: 423.1964, found 423.1974

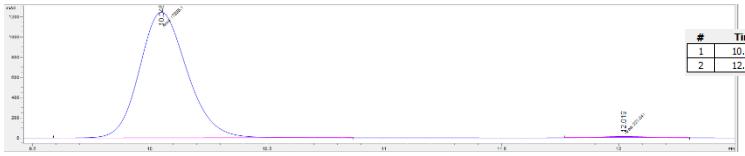
M.P. 90–92 ºC (EtOAc)

R_f = 0.15 (Pentane:EtOAc = 85:15)

Chiral HPLC: (Daicel Chiralcel-IA column (25 cm) with guard, hexane:isopropanol = 95:5, 1.0 mL/min, room temperature, 210.8 nm): tR = 10.05 minutes (major), 12.02 minutes (minor), e.r. = 99:1

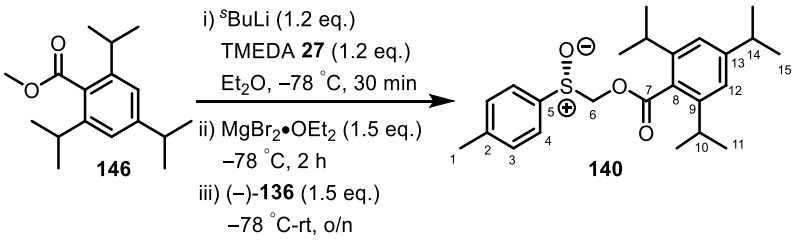


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.06	MM	4487.7	316.6	0.2363	49.768	0.863
2	12.023	MM	4529.7	264.4	0.2855	50.232	0.873



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.048	MM	17885.1	1255.6	0.2374	98.779	0.822
2	12.019	MM	221	13.5	0.273	1.221	1.051

(*S*)-(*p*-Tolylsulfinyl)methyl 2,4,6-triisopropylbenzoate *ent*-(**140**)

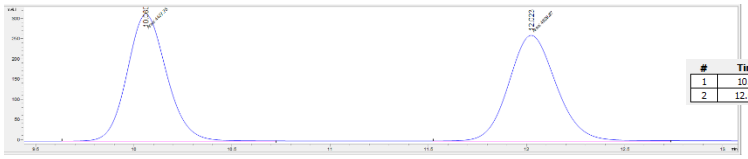


Following **GP1**, methyl benzoate **146** (5.00 g, 19.1 mmol), TMEDA **27** (3.71 mL, 24.8 mmol), ^{s}BuLi (1.30 M in cyclohexane/hexane, 19.1 mL, 24.8 mmol – lithiation time = 30 min), Mg turnings (1.37 g, 57.2 mmol), dibromoethane (2.46 mL, 28.6 mmol) and (1*R*,2*S*,5*R*)-(–)-menthyl (*S*)-*p*-toluenesulfinate (**136**) (8.15 g, 28.6 mmol) afforded after purification by flash column chromatography (Hexane:EtOAc = 100:0 → 80:20) α-sulfinyl benzoate *ent*-**140** (5.09 g, 67%) as a white solid.

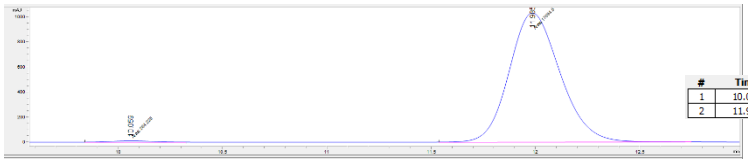
[α]$^{22}_{D}$: + 134 ° (*c* 1.0, $CHCl_3$)

Spectral data in accordance with that described above.

Chiral HPLC: (Daicel Chiralcel-IA column (25 cm) with guard, hexane:isopropanol = 95:5, 1.0 mL/min, room temperature, 210.8 nm): tR = 10.06 minutes (minor), 12.02 minutes (major), e.r. = 99:1

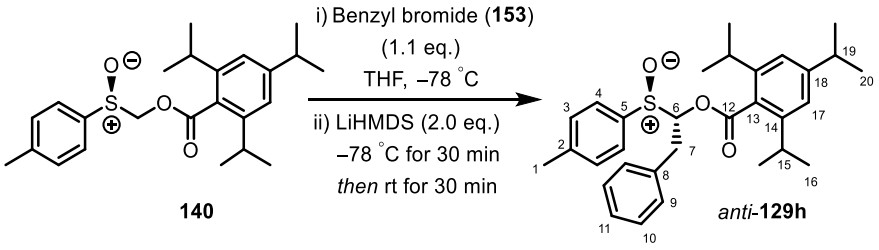


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.06	MM	4487.7	316.6	0.2363	49.768	0.863
2	12.023	MM	4529.7	264.4	0.2855	50.232	0.873



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.059	MM	264.2	14.5	0.3035	1.471	0.841
2	11.985	MM	17694.5	1032.1	0.2857	98.529	0.819

(*S*)-2-Phenyl-1-((*R*)-*p*-tolylsulfinyl)ethyl 2,4,6-triisopropylbenzoate *anti*-(**129h**)



According to **GP2** using ((*R*)-*p*-tolylsulfinyl) methyl 2,4,6-triisopropylbenzoate **140** (400 mg, 1.00 mmol), LiHMDS (1.0 M in THF, 2.00 mL, 2.00 mmol) and benzyl bromide (**153**) (140 µL, 1.10 mmol). The crude residue (91:9 d.r.) was purified by silica gel chromatography (Pentane:EtOAc = 100:0 → 91:9) which gave *anti*-**129h** (311 mg, 63%) as a colourless oil.

[α]$^{22}_{D}$: + 45 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.0 Hz, 2H, H-4), 7.36–7.20 (m, 7H, H-3, H-9, H-10 and H-11), 6.97 (s, 2H, H-17), 6.37 (dd, J_1 = 10.0 Hz, J_2 = 3.7 Hz, 1H, H-6), 3.32 (dd, J_1 = 14.6 Hz, J_2 = 3.7 Hz, 1H, H-7a), 2.88 (sept, *J* = 6.8 Hz, 1H, H-19), 2.59 (dd, J_1 = 14.6 Hz, J_2 =10.0 Hz, 1H, H-7b), 2.47 (sept, *J* = 6.8 Hz, 2H, H-15), 2.43 (s, 3H, H-1), 1.24 (d, *J* = 6.8 Hz, 6H, H-20), 1.09 (d, *J* = 6.8 Hz, 6H, H-16a), 1.07 (d, *J* = 6.8 Hz, 6H, H-16b) ppm

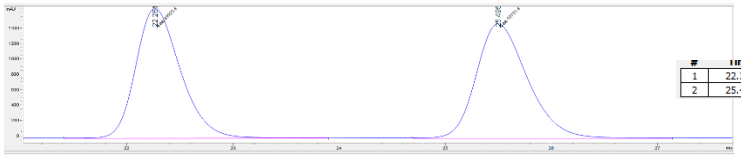
^{13}C NMR (101 MHz, $CDCl_3$): 169.2 (CO), 150.8 (C), 145.3 (2 × C), 142.3 (C), 136.2 (C), 135.1 (C), 130.1 (2 × CH), 129.3 (2 × CH), 128.9 (C), 128.8 (2 × CH), 127.3 (CH), 125.6 (2 × CH), 121.0 (2 × CH), 88.3 (CH), 34.5 (CH), 33.4 (CH_2), 31.4 (2 × CH), 24.5 (2 × CH_3), 24.3 (2 × CH_3), 24.0 (2 × CH_3), 21.6 (CH_3) ppm

IR (neat): 2965, 2233, 1734, 1233, 1031, 730 cm^{-1}

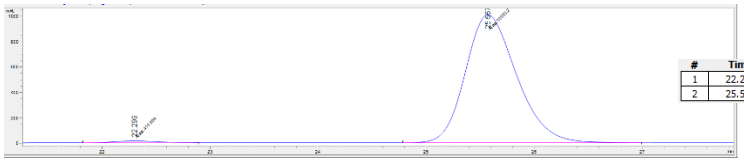
HRMS (ESI) calculated for $C_{31}H_{38}O_3SNa$: 513.2434, found 513.2442

R_f = 0.23 (Pentane:EtOAc = 85:15)

Chiral HPLC: (Daicel Chiralcel-IA column (25 cm) with guard, hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm): tR = 22.30 minutes (minor), 25.57 minutes (major), e.r. = 99:1

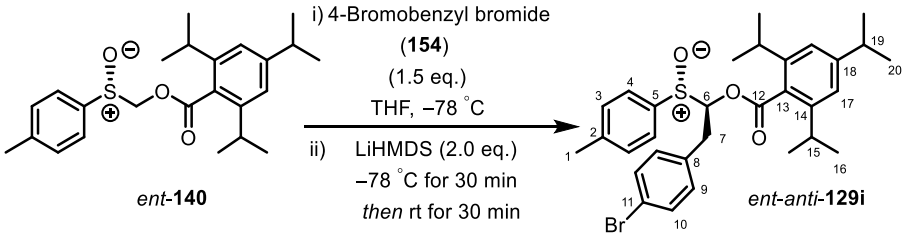


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	22.261	MM	49923.4	1687.2	0.4932	49.613	0.733
2	25.495	MM	50701.4	1488.9	0.5676	50.387	0.723



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	22.299	MM	415.9	14.8	0.4674	1.224	0.981
2	25.567	MM	33553.2	1007.7	0.555	98.776	0.761

(*R*)-2-(4-Bromophenyl)-1-((*S*)-*p*-tolylsulfinyl)ethyl 2,4,6-triisopropylbenzoate *ent-anti*-(**129i**)



According to **GP2** using ((*S*)-*p*-tolylsulfinyl)methyl 2,4,6-triisopropylbenzoate *ent*-**140** (1.00 g, 2.50 mmol), LiHMDS (1.0 M in THF, 5.00 mL, 5.00 mmol) and 4-bromobenzyl bromide (**154**) (929 mg, 3.75 mmol). The crude residue (d.r. = 15:1) was purified by silica gel chromatography (Pentane:EtOAc = 100:0 → 91:9) which gave *ent-anti*-**129i** (568 mg, 40%) as a white crystalline solid.

$[\alpha]^{22}_{D}$: – 82 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.1 Hz, 2H, H-10), 7.42 (d, *J* = 8.3 Hz, 2H, H-4), 7.34 (d, *J* = 8.1 Hz, 2H, H-9), 7.08 (d, *J* = 8.3 Hz, 2H, H-3), 6.96 (s, 2H, H-17), 6.31 (dd, J_1 = 10.2 Hz, J_2 = 3.8 Hz, 1H, H-6), 3.25 (dd, J_1 = 14.4 Hz, J_2 = 3.8 Hz, 1H, H-7a), 2.87 (sept, *J* = 6.8 Hz, 1H, H-19), 2.50 (dd, J_1 = 14.4 Hz, J_2 =10.2 Hz, 1H, H-7b), 2.43 (s, 3H, H-1), 2.41 (sept, *J* = 6.8 Hz, 2H, H-15), 1.23 (d, *J* = 6.8 Hz, 6H, H-20), 1.10 (d, *J* = 6.8 Hz, 6H, H-16a) 1.08 (d, *J* = 6.8 Hz, 6H, H-16b) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 169.1 (CO), 150.9 (C), 145.3 (C), 142.4 (C), 136.0 (C), 134.2 (C), 131.9 (2 × CH), 131.1 (2 × CH), 130.2 (2 × CH), 128.7 (C), 125.6 (2 × CH), 127.3 (CH), 121.3 (C), 121.0 (2 × CH), 87.9 (CH), 34.5 (CH), 32.8 (CH_2), 31.5 (2 × CH), 24.4 (2 × CH_3), 24.3 (2 × CH_3), 24.0 (2 × CH_3), 21.6 (CH_3) ppm

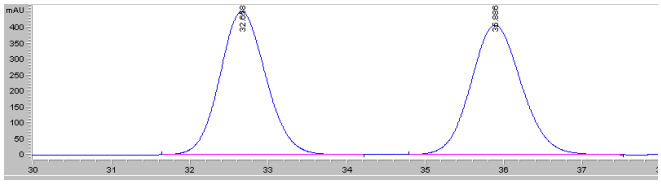
IR (neat): 2962, 1736, 1229, 1039, 810 cm^{-1}

HRMS (ESI) calculated for $C_{31}H_{37}{}^{79}BrO_3SNa$: 591.1539, found 591.1541

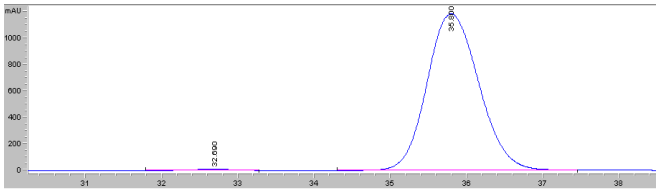
M.P. 114–116 ºC (EtOAc)

R_f = 0.31 (Pentane:EtOAc = 85:15)

Chiral HPLC: (Daicel Chiralcel-IA column (25 cm) with guard, hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm): tR = 32.70 minutes (minor), 35.80 minutes (major), e.r. >99:1

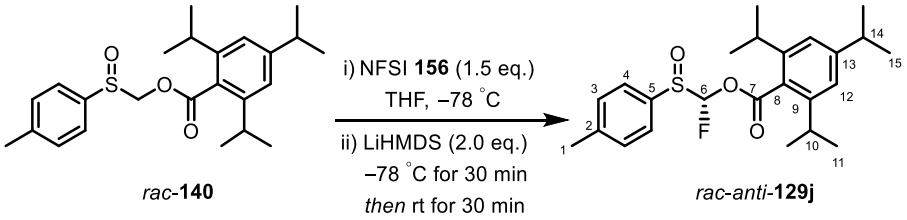


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	A
1	32.658	BB	0.6374	1.84946e4	451.94720	50
2	35.886	BP	0.6962	1.83782e4	408.99823	49



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.690	BV	0.4772	398.13724	9.98506	0.7056
2	35.800	VB	0.6425	5.60285e4	1183.17224	99.2944

Fluoro(*p*-tolylsulfinyl)methyl 2,4,6-triisopropylbenzoate *rac-anti*-(**129j**)



According to **GP2** using (*p*-tolylsulfinyl)methyl 2,4,6-triisopropylbenzoate *rac*-**140** (600 mg, 1.50 mmol), LiHMDS (1.0 M in THF, 3.00 mL, 3.00 mmol) and *N*-fluorobenzenesulfonimide (**142**) (946 mg, 3.00 mmol). The crude residue (10:1 d.r.) was purified by silica gel chromatography (Pentane:EtOAc = 100:0 → 93:7) which gave *rac-anti*-**129j** (201 mg, 32%) as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.3 Hz, 2H, H-4), 7.34 (d, *J* = 8.3 Hz, 2H, H-3), 7.00 (s, 2H, H-12), 6.89 (d, $^{2}J_{HF}$ = 54.6 Hz, 1H, H-6), 2.88 (sept, *J* = 7.0 Hz, 1H, H-14), 2.52 (sept, *J* = 6.8 Hz, 2H, H-10), 2.44 (s, 3H, H-1), 1.24 (d, *J* = 7.0 Hz, 6H, H-15), 1.14 (d, *J* = 6.8 Hz, 6H, H-11a), 1.12 (d, *J* = 6.8 Hz, 6H, H-11b).

^{13}C NMR (101 MHz, $CDCl_3$): 167.2 (CO), 151.7 (C), 145.6 (2 × C), 143.6 (C), 134.8 (C), 130.3 (2 × CH), 127.0 (C), 126.3 (2 × CH), 121.1 (2 × CH), 110.6 (d, $^{1}J_{CF}$ = 266.0 Hz, CHF), 34.5 (CH), 31.5 (2 × CH), 24.4 (2 × CH_3), 23.9 (4 × CH_3), 21.7 (CH_3)

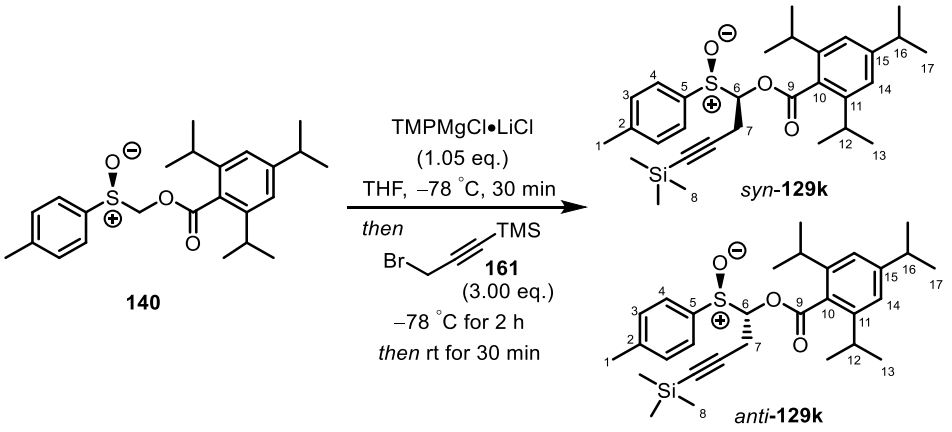
^{19}F NMR (377 MHz, $CDCl_3$) –131.5 (d, $^{2}J_{FH}$ = 54.6 Hz, 1F)

HRMS (ESI^+): calculated for $C_{24}H_{31}{}^{19}FO_3SNa$: 441.1883; found 441.1870.

IR (ν_{max}/cm^{-1}, neat): 2963, 1771, 1221, 1052, 813 cm^{-1}

R_f = 0.51 (Pentane:EtOAc = 85:15)

(*R*)-1-((*R*)-*p*-Tolylsulfinyl)-4-(trimethylsilyl)but-3-yn-1-yl2,4,6-triisopropylbenzoate *syn*-(**129k**) **and (*S*)-1-((*R*)-*p*-tolylsulfinyl)-4-(trimethylsilyl)but-3-yn-1-yl 2,4,6-triisopropylbenzoate** *anti*-(**129k**)



((*R*)-*p*-Tolylsulfinyl)methyl 2,4,6-triisopropylbenzoate **140** (400 mg, 1.00 mmol) in an oven dried Schlenk tube was dissolved in anhydrous THF (4.00 mL). The solution was cooled to –78 °C and 2,2,6,6-tetramethylpiperidinylmagnesium chloride lithium chloride complex (1.0 M in THF/toluene, 1.05 mL, 1.05 mmol) was added dropwise (0.2 mL/min). The solution was stirred for 20 min, at which point a solution of 3-bromo-1-(trimethylsilyl)-1-propyne (**161**) (495 μL, 3.00 mmol) in THF (1.0 mL) was added dropwise. The reaction mixture was stirred at –78 °C for a further 2 h and then the cooling bath was removed, and the solution was stirred at room temperature for 30 min. The reaction mixture was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and diluted with EtOAc (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude residue (d.r. = 2.5:1) was purified by silica gel chromatography (Pentane:EtOAc = 100:0 → 93:7) which gave *syn*-**129k** (*less polar*, 160 mg, 31%) and *anti*-**129k** (*more polar*, 70.0 mg, 14%) as white amorphous solids. Further elution (Pentane:EtOAc = 93:7 → 75:25) gave recovered starting material **140** (154 mg, 39%) as a white crystalline solid.

syn-**129k**

$[\alpha]^{22}_D$: – 40 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.8 Hz, 2H, H-4), 7.37 (d, *J* = 8.8 Hz, 2H, H-3), 7.05 (s, 2H, H-14), 5.84 (dd, J_1 = 8.7 Hz, J_2 = 3.8 Hz, 1H, H-6), 3.02-2.82 (m, 4H, H-

7a, H-12 and H-16), 2.72 (dd, J_1 = 18.0 Hz, J_2 = 3.8 Hz, 1H, H-7b), 2.45 (s, 3H, H-1), 1.30–1.25 (m, 18H, H-13 and H-17), 0.08 (s, 9H, H-8) ppm

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1 (CO), 151.2 (C), 145.6 (2 × C), 142.1 (C), 137.0 (C), 130.3 (2 × CH), 128.6 (C), 124.7 (2 × CH), 121.2 (2 × CH), 100.0 (C), 90.3 (CH), 88.1 (C), 34.6 (CH), 31.6 (2 × CH), 24.6 (2 × CH_3), 24.4 (2 × CH_3), 24.0 (2 × CH_3), 21.6 (CH_3), 16.4 (CH_2), 0.0 (3 × CH_3) ppm

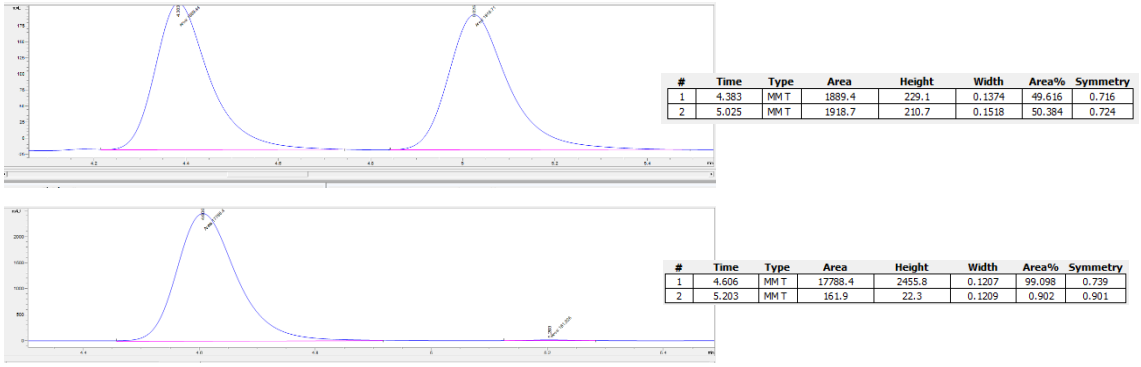
IR (neat): 2961, 2182, 1736, 1041, 837 cm^{-1}

HRMS (ESI) calculated for $C_{30}H_{42}O_3SSiNa$: 533.2516, found 533.2504

R_f = 0.55 (Pentane:EtOAc = 85:15)

Chiral HPLC: (Daicel Chiralcel-IA column (25 cm) with guard, hexane:isopropanol = 95:5, 1.0 mL/min, room temperature, 210.8 nm): tR = 4.60 minutes (major), 5.20 minutes (minor), e.r. > 99:1

*Note: ent-syn **114k** decomposes at room temperature and should be stored in a freezer where it is stable for over several months.*



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.383	MM T	1889.4	229.1	0.1374	49.616	0.716
2	5.025	MM T	1918.7	210.7	0.1518	50.384	0.724

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.606	MM T	17788.4	2455.8	0.1207	99.098	0.739
2	5.203	MM T	161.9	22.3	0.1209	0.902	0.901

anti-**129k**

[α]$^{22}_D$: + 29 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.4 Hz, 2H, H-4), 7.31 (d, *J* = 8.4 Hz, 2H, H-3), 7.02 (s, 2H, H-14), 6.06 (dd, J_1 = 7.4 Hz, J_2 = 4.4 Hz, 1H, H-6), 2.96 (dd, J_1 = 17.5 Hz, J_2 = 4.4 Hz, 1H, H-7a), 2.92–2.78 (m, 3H, H-12 and H-16), 2.41 (s, 3H, CH_3), 2.31 (dd, J_1 = 17.5 Hz, J_2 = 7.4 Hz, 1H, H-7b), 1.27–1.18 (m, 18H, H-13 and H-17), 0.15 (s, 9H, H-8) ppm

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0 (CO), 151.0 (C), 145.5 (2 × C), 142.4 (C), 136.0 (C), 130.1 (2 × CH), 128.6 (C), 125.5 (2 × CH), 121.1 (2 × CH), 99.5 (C), 89.0 (C), 86.5

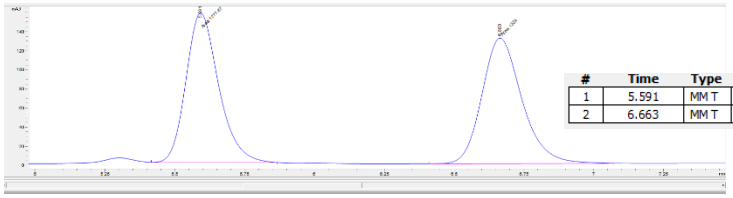
(CH), 34.6 (CH), 31.7 (2 × CH), 25.0 (2 × CH_3), 24.0 (4 × CH_3), 21.6 (CH_3), 20.2 (CH_2), 0.0 (3 × CH_3) ppm

IR (neat): 2967, 2181, 1746, 1054, 839 cm^{-1}

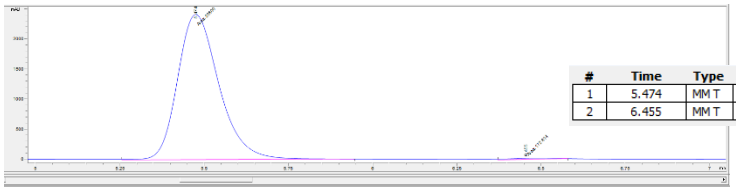
HRMS (ESI) calculated for $C_{30}H_{42}O_3SSiNa$: 533.2516, found 533.2510

R_f = 0.48 (Pentane:EtOAc = 85:15)

Chiral HPLC: (Daicel Chiralcel-IA column (25 cm) with guard, hexane:isopropanol = 95:5, 1.0 mL/min, room temperature, 210.8 nm): tR = 5.47 minutes (major), 6.46 minutes (minor), e.r. > 99:1

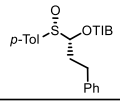
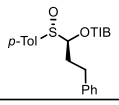
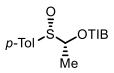
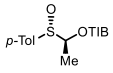
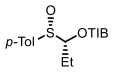
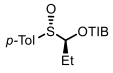
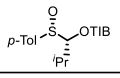
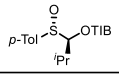
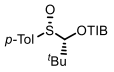
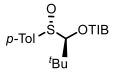
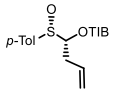
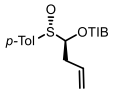
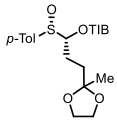
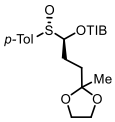
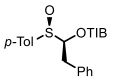
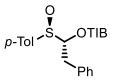


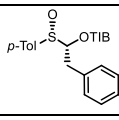
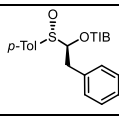
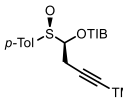
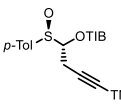
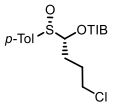
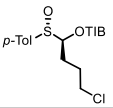
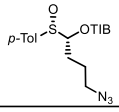
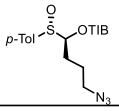
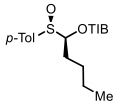
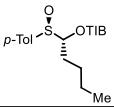
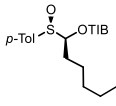
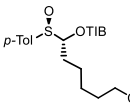
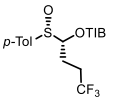
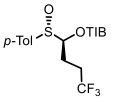
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.591	MM T	1277.9	156.6	0.136	49.113	0.79
2	6.663	MM T	1324	131.6	0.1676	50.887	0.802



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.474	MM T	20800	2416.8	0.1434	99.176	0.75
2	6.455	MM T	172.8	19.8	0.1523	0.824	0

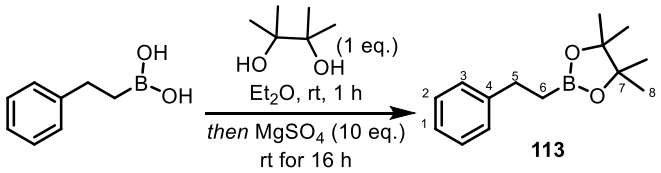
Table S1. Correlation between the chemical shifts of the α_H/α_C of sulfinyl benzoates and relative configuration

syn-14 (less polar)	*anti*-14 (more polar)
 α_H 5.64 ppm, α_C 92.0 ppm	 α_H 6.08 ppm, α_C 87.8 ppm
 α_H 5.79 ppm, α_C 89.0 ppm	 α_H 6.07 ppm, α_C 85.0 ppm
 α_H 5.62 ppm, α_C 93.8 ppm	 α_H 5.93 ppm, α_C 89.9 ppm
 α_H 5.72 ppm, α_C 95.8 ppm	 α_H 5.89 ppm, α_C 94.5 ppm
 α_H 5.61 ppm, α_C 98.6 ppm	 α_H 5.66 ppm, α_C 95.7 ppm
 α_H 5.75 ppm, α_C 91.3 ppm	 α_H 6.07 ppm, α_C 87.2 ppm
 α_H 5.78 ppm, α_C 92.5 ppm	 α_H 6.09 ppm, α_C 88.4 ppm
 α_H 5.99 ppm, α_C N.D.	 α_H 6.37 ppm, α_C 88.3 ppm

syn-14 (less polar)	*anti*-14 (more polar)
 α_H 5.92 ppm, α_C N.D.	 α_H 6.31 ppm, α_C 87.9 ppm
 α_H 5.84 ppm, α_C 90.3 ppm	 α_H 6.06 ppm, α_C 89.0 ppm
 α_H 5.68 ppm, α_C N.D.	 α_H 6.02 ppm, α_C 87.6 ppm
 α_H 5.67 ppm, α_C 92.1 ppm	 α_H 6.01 ppm, α_C 87.8 ppm
 α_H 5.67 ppm, α_C 92.5 ppm	 α_H 6.00 ppm, α_C 88.5 ppm
 α_H 5.66 ppm, α_C 92.5 ppm	 α_H 5.99 ppm, α_C 88.7 ppm
 α_H 5.68 ppm, α_C 90.7 ppm	 α_H 6.03 ppm, α_C N.D.

most down-field most up-field

4,4,5,5-tetramethyl-2-phenethyl-1,3,2-dioxaborolane (113)



113

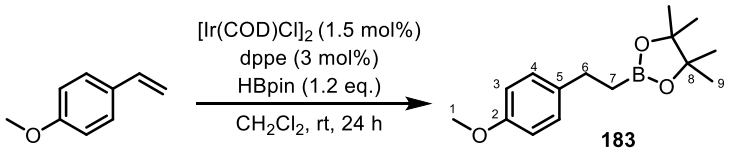
Prepared according to Aggarwal *et al.*[199]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.11 (m, 5H, H-1, H-2 and H-3), 2.74 (t, *J* = 8.2 Hz, 2H, H-5), 1.22 (s, 12H, H-8), 1.12 (t, *J* = 8.2 Hz, 2H, H-6)

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.5 (C), 128.3 (2 × CH), 128.1 (2 × CH), 125.6 (CH), 83.2 (2 × C), 30.1 (CH_2), 25.0 (4 × CH_3) (*Carbon attached to boron not observed due to quadrupolar relaxation*).

Data in accordance with that reported in the literature.[199]

2-(4-Methoxyphenethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**183**)



Prepared according to Yamamoto *et al.*[200]

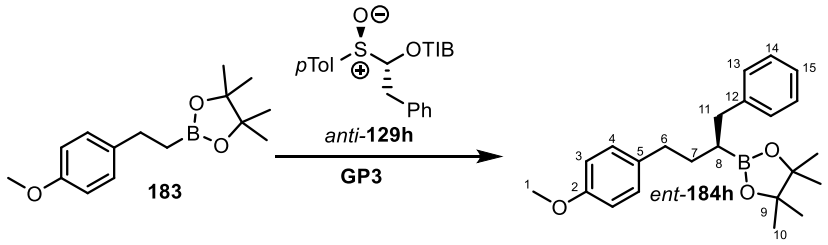
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J* = 8.8 Hz, 2H, H-4), 6.81 (d, *J* = 8.8 Hz, 2H, H-3), 3.77 (s, 3H, H-1), 2.69 (t, *J* = 8.0 Hz, 2H, H-6), 2.10 (t, *J* = 8.0 Hz, 2H, H-7), 1.22 (s, 12H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.7 (C), 136.7 (C), 129.0 (2 × CH), 113.7 (2 × CH), 83.2 (2 × C), 55.4 (CH_3), 29.2 (CH_2), 25.0 (4 × CH_3) (*Carbon attached to boron not observed due to quadrupolar relaxation*).

Data in accordance with that reported in the literature.[200]

(1,2-bis(diphenylphosphino)ethane (dppe))

(*S*)-2-(4-(4-methoxyphenyl)-1-phenylbutan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane *ent*-(**184h**) **and (*S*)-4-(4-methoxyphenyl)-1-phenylbutan-2-ol** *ent*-[O]-(**184h**)



Following **GP3**, benzyl sulfoxide *anti*-**129h** (108 mg, 0.22 mmol), boronic ester **183** (52.4 mg, 0.20 mmol) and ^{t}BuLi (1.7 M in pentane, 235 µL, 0.40 mmol), filtered through basic silica, afforded after purification by flash column chromatography (Pentane:Et_2O = 95:5) the homologated boronic ester *ent*-**184h** (58 mg, 79%) as a colourless oil.

[α]$^{22}_{D}$: – 31 ° (*c* 0.9, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.17 (m, 4H, H-13 and H-14), 7.14 (tt, 1H, J_1 = 6.9 Hz, J_2 = 2.6 Hz, H-15), 7.07 (d, *J* = 8.5 Hz, 2H, H-4), 6.82 (d, *J* = 8.5 Hz, 2H, H-3), 3.78 (s, 3H, H-1), 2.78–2.68 (m, 2H, H-6a and 11a), 2.65–2.50 (m, 2H, H-6b and 11b), 1.78–1.61 (m, 2H, H-7), 1.44 (pent, *J* = 6.0 Hz, 1H, H-8), 1.18 (s, 6H, H-10a), 1.15 (s, 6H, H-10b) ppm

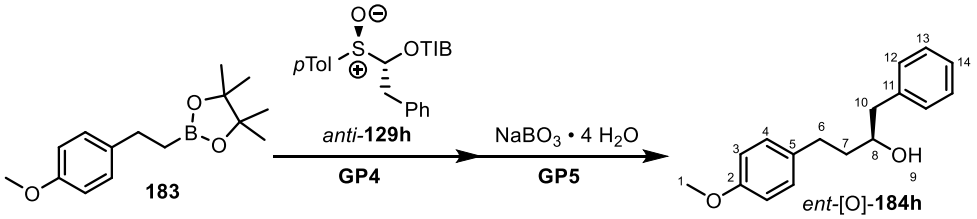
^{13}C NMR (101 MHz, $CDCl_3$): 157.5 (C) 141.9 (C), 134.7 (C), 129.1 (2 × CH), 128.7 (2 × CH), 127.9 (2 × CH), 125.4 (CH), 113.5 (2 × CH), 82.9 (2 × C), 55.1 (CH_3), 37.0 (CH_2), 34.4 (CH_2), 33.2 (CH_2), 25.4 (CH), 24.7 (2 × CH_3), 24.6 (2 × CH_3) ppm

^{11}B NMR (96 MHz): 32.9 ppm

IR (neat): 2977, 2924, 1511, 1370, 1244, 1143, 1037 cm^{-1}

HRMS (ESI) calculated for $C_{23}H_{31}BO_3Na$: 389.2263, found 389.2264

R_f = 0.20 (Pentane:Et_2O = 95:5)



Following **GP4**, benzyl sulfoxide *anti*-**129h** (128 mg, 0.26 mmol), boronic ester **183** (52.4 mg, 0.2 mmol) and ^{i}PrMgCl•LiCl (1.14 M in THF, 210 µL, 0.24 mmol), filtered through basic silica, afforded after purification by flash column chromatography (Pentane:Et_2O =

95:5) a mixture of the homologated boronic ester *ent*-**184h** and starting boronic ester **183**. Following **GP5**, oxidation of the mixture using $NaBO_3$•$4H_2O$ (308 mg, 2.00 mmol), afforded after purification by flash column chromatography (Pentane:EtOAc = 80:20) the corresponding alcohol *ent*-[O]-**184h** (33 mg, 58%) as a colourless oil.

[α]$^{22}_D$: – 17 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.29 (m, 2H, H-12), 7.27–7.18 (m, 3H, H-13 and H-14), 7.12 (d, J = 8.3 Hz, 2H, H-4), 6.84 (d, J = 8.3 Hz, 2H, H-3), 3.84 (m, 1H, H-8), 3.79 (s, 3H, H-1), 2.85 (dd, J_1 = 13.8 Hz, J_2 = 4.2 Hz, 1H, H-10a), 2.78 (m, 1H, H-6a), 2.73–2.62 (m, 2H, H-10b and H-6b), 1.85–1.78 (m, 2H, H-7), 1.52 (br. s, 1H, H-9) ppm

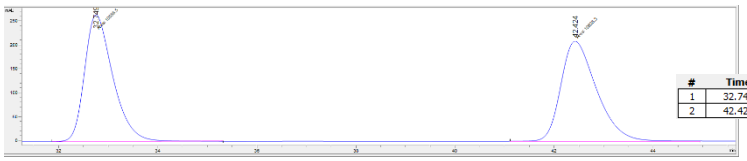
^{13}C NMR (101 MHz, $CDCl_3$): 157.9 (C), 138.5 (C), 134.2 (C), 129.6 (2 × CH), 129.5 (2 × CH), 128.7 (2 × CH), 126.6 (CH), 114.0 (2 × CH), 72.1 (CH), 55.4 (CH_3), 44.3 (CH_2), 38.8 (CH_2), 31.3 (CH_2) ppm

IR (neat): 3407 (br), 2933, 1511, 1243, 1034, 823 cm^{-1}

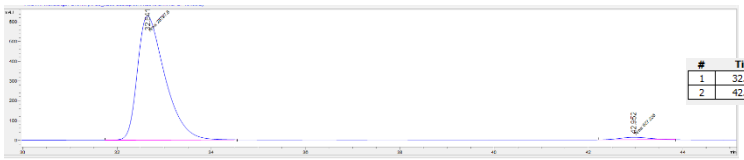
HRMS (ESI) calculated for $C_{17}H_{20}O_2Na$: 279.1356, found 279.1351

R_f = 0.17 (Pentane:EtOAc = 80:20)

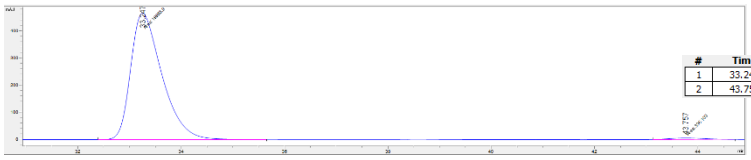
Chiral HPLC: (Daicel Chiralcel-IB column (25 cm) with guard, hexane:isopropanol = 98:2, 0.5 mL/min, room temperature, 210.8 nm): tR = 32.7 minutes (major), 42.4 minutes (minor), e.r. = 98:2 (Li), e.r. = 98:2 (Mg)



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	32.749	MM	10556.5	265	0.6638	49.814	0.666
2	42.424	MM	10635.3	209.5	0.8462	50.186	0.644

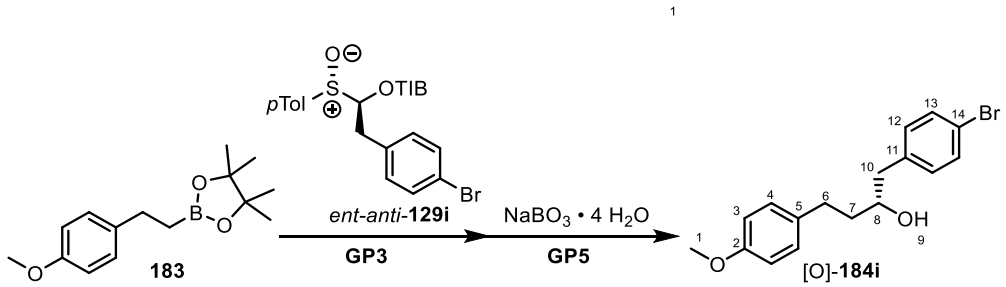


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	32.641	MM	25797.6	629.7	0.6828	97.626	0.561
2	42.952	MM	627.2	13	0.8014	2.374	0.849



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	33.247	MM	19965.9	468.4	0.7104	98.055	0.589
2	43.757	MM	396.1	7.1	0.9349	1.945	0.884

(*R*)-2-(1-(4-bromophenyl)-4-(4-methoxyphenyl)butan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**184i**) **and (*R*)-1-(4-bromophenyl)-4-(4-methoxyphenyl)butan-2-ol** [O]-(**184i**)



Following modified **GP3**, *p*-bromobenzyl sulfoxide *ent-anti*-**129i** (125 mg, 0.22 mmol), boronic ester **170** (52.4 mg, 0.20 mmol), and ^{t}BuLi (1.7 M in pentane, 142 µL, 0.24 mmol), filtered through basic silica, afforded after purification by flash column chromatography (Pentane:Et_2O = 95:5) a mixture of the homologated boronic ester **184i** and starting boronic ester **183**. Following **GP5**, oxidation of the mixture using $NaBO_3$•$4H_2O$ (308 mg, 2.00 mmol), afforded after purification by flash column chromatography (Pentane:EtOAc = 80:20) the alcohol [O]-**184i** (24 mg, 36%) as a white solid.

[α]$^{22}_{D}$: + 20 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.2 Hz, 2H, H-13), 7.10 (d, *J* = 8.6 Hz, 2H, H-4), 7.08 (d, *J* = 8.2 Hz, 2H, H-12), 6.83 (d, *J* = 8.6 Hz, 2H, H-3), 3.80 (m, 1H, H-8), 3.79 (s, 3H, H-1), 2.81–2.76 (m, 2H, H-6a and H-10a), 2.69–2.61 (m, 2H, H-6b and H-10b), 1.84–1.74 (m, 2H, H-7), 1.46 (br. d, *J* = 3.6 Hz, 1H, H-9)

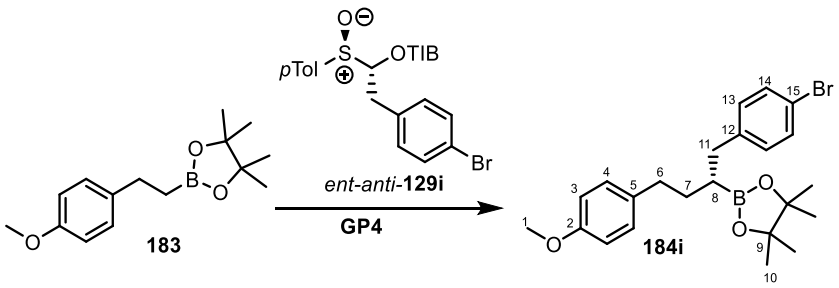
^{13}C NMR (101 MHz, $CDCl_3$): 158.0 (C), 137.6 (C), 133.9 (C), 131.7 (2 × CH), 131.3 (2 × CH), 129.4 (2 × CH), 120.5 (C) 114.0 (2 × CH), 71.9 (CH), 55.4 (CH_3), 43.6 (CH_2), 38.8 (CH_2), 31.3 (CH_2)

IR (neat): 3320, 2945, 1512, 1247, 1012, 802 cm^{-1}

HRMS (ESI) calculated for $C_{17}H_{19}{}^{79}BrO_2Na$: 357.0461, found 357.0456

M.P. 72–74 ºC (EtOAc)

R_f = 0.19 (Pentane:EtOAc = 80:20)



Following **GP4**, *p*-bromobenzyl sulfoxide *ent-anti*-**129i** (148 mg, 0.26 mmol), boronic ester **183** (52.4 mg, 0.20 mmol) and ^{i}PrMgCl•LiCl (1.14 M in THF, 210 µL, 0.24 mmol), filtered through basic silica, afforded after purification by flash column chromatography (Pentane:Et_2O = 95:5) the homologated boronic ester **184i** (72 mg, 81%) as a colourless oil.

[α]$^{22}_{D}$: + 15 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.3 Hz, 2H, H-14), 7.09–7.04 (m, 4H, H-4 and H-13), 6.81 (d, *J* = 8.0 Hz, 2H, H-3), 3.78 (s, 3H, H-1), 2.74–2.47 (m, 4H, H-6 and H-11), 1.78–1.58 (m, 2H, H-7), 1.44 (pent, 1H, *J* = 7.5 Hz, H-8), 1.19 (s, 6H, H-10a), 1.17 (s, 6H, H-10b) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 157.9 (C) 141.2 (C), 134.8 (C), 131.2 (2 × CH), 130.8 (2 × CH), 129.4 (2 × CH), 119.5 (C), 113.8 (2 × CH), 83.3 (2 × C), 55.4 (CH_3), 36.7 (CH_2), 34.6 (CH_2), 33.4 (CH_2), 25.5 (CH), 25.0 (2 × CH_3), 24.9 (2 × CH_3) ppm

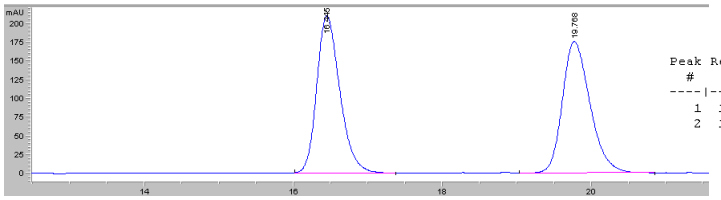
^{11}B NMR (96 MHz): 33.5 ppm

IR (neat): 2982, 2935, 1511, 1379, 1244, 1142, 824 cm^{-1}

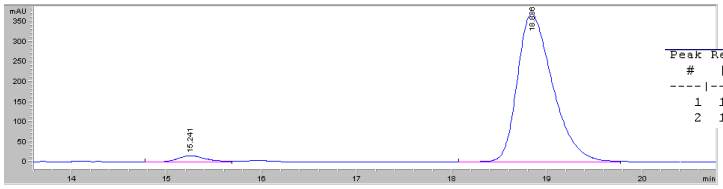
HRMS (ESI) calculated for $C_{23}H_{30}B^{79}BrO_3Na$: 467.1368, found 467.1381

R_f = 0.14 (Pentane:Et_2O = 95:5)

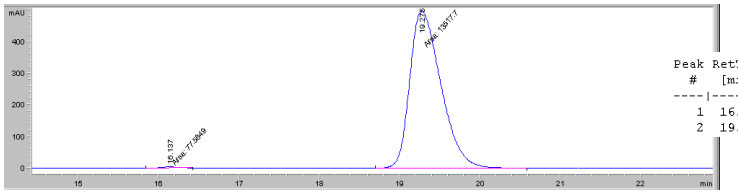
Chiral HPLC: (Daicel Chiralcel-IB column (25 cm) with guard, hexane:isopropanol = 96:4, 1.0 mL/min, room temperature, 210.8 nm): tR = 16.4 minutes (minor), 19.8 minutes (major), e.r. = 97:3 (Li), e.r. > 99:1 (Mg)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.445	BB	0.3317	4534.43652	210.19647	49.9442
2	19.768	VB	0.4021	4544.57178	175.48772	50.0558

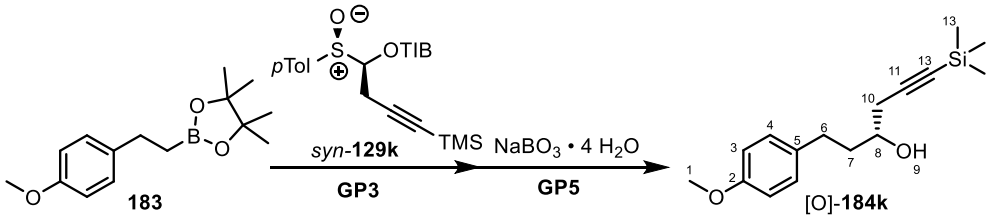


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.241	VV	0.2975	320.99515	15.76789	3.2428
2	18.836	VV	0.3924	9577.67090	369.48154	96.7572

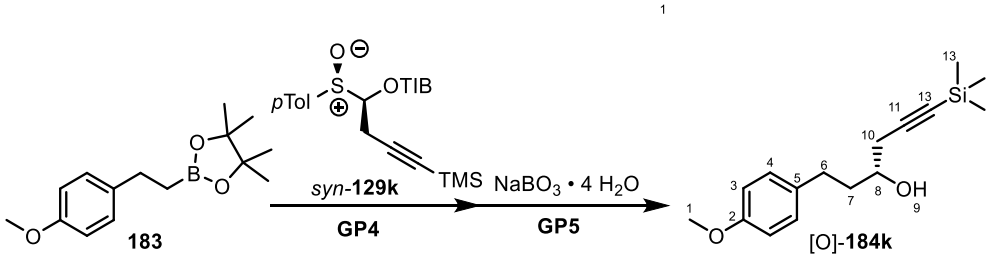


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.137	MM	0.2931	77.56490	4.41115	0.5705
2	19.275	MM	0.4509	1.35177e4	499.63275	99.4295

(*R*)-1-(4-methoxyphenyl)-6-(trimethylsilyl)hex-5-yn-3-ol *ent*-[O]-(**184k**)



Following **GP3**, alkynyl sulfoxide *syn*-**129k** (112 mg, 0.22 mmol), boronic ester **183** (52.4 mg, 0.20 mmol), ^{t}BuLi (1.7 M in pentane, 235 µL, 0.40 mmol), afforded after purification by flash column chromatography (Pentane:Et_2O = 95:5) a mixture of the homologated boronic ester **184k** and starting boronic ester **183**. Following **GP5**, oxidation of the mixture using $NaBO_3$•$4H_2O$ (308 mg, 2.00 mmol) afforded after purification by flash column chromatography (Pentane:EtOAc = 100:0 → 85:15) the alcohol [O]-**184k** (30 mg, 54%) as a colourless oil.



Following **GP4**, alkynyl sulfoxide *syn*-**129k** (133 mg, 0.26 mmol), boronic ester **183** (52.4 mg, 0.20 mmol) and ^{i}PrMgCl•LiCl (1.14 M in THF, 210 µL, 0.24 mmol) afforded after purification by flash column chromatography (Pentane:Et_2O = 95:5) a mixture of the desired homologated boronic ester **184k** and starting boronic ester **183**. Following **GP5**, oxidation of the mixture using $NaBO_3$•$4H_2O$ (308 mg, 2.00 mmol) afforded after purification by flash column chromatography (Pentane/EtOAc = 100:0 → 85:15) the alcohol [O]-**184k** (33 mg, 60%) as a colourless oil.

[α]$^{22}_{D}$: + 7 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J* = 8.6 Hz, 2H, H-4), 6.84 (d, *J* = 8.6 Hz, 2H, H-3), 3.79 (s, 3H, H-1), 3.74 (app. br. pent., *J* = 6.0 Hz, 1H, H-8), 2.74 (dt, J_1 = 13.9 Hz, J_2 = 7.5 Hz, 1H, H-6a), 2.64 (dt, J_1 = 13.9 Hz, J_2 = 8.1 Hz, 1H, H-6b), 2.47 (dd, J_1 = 17.1 Hz, J_2 = 4.8 Hz, 1H, H-10a), 2.38 (dd, J_1 = 17.1 Hz, J_2 = 6.8 Hz, 1H, H-10b), 2.00 (br. s, 1H, H-9), 1.82 (dt, J_1 = 8.1 Hz, J_2 = 6.0 Hz, 2H, H-7), 0.16 (s, 9H, H-11) ppm

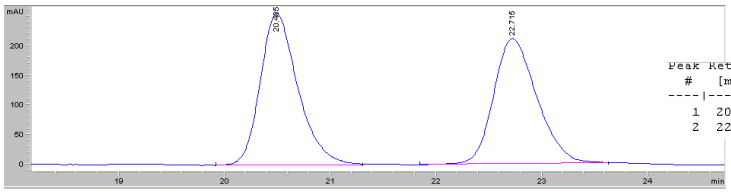
^{13}C NMR (101 MHz, $CDCl_3$): 158.0 (C), 133.9 (C), 129.4 (2 × CH), 114.0 (2 × CH), 103.2 (C), 87.9 (C), 69.2 (CH), 55.4 (CH_3), 38.1 (CH_2), 31.1 (CH_2), 29.1 (CH_2), 0.2 (3 × CH_3) ppm

IR (neat): 3389, 2954, 2173, 1512, 1246, 841 cm^{-1}

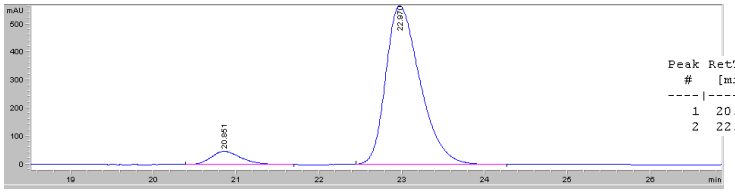
HRMS (ESI) calculated for $C_{16}H_{24}O_2SiNa$: 299.1546, found 299.1534

R_f = 0.19 (Pentane:EtOAc = 80:20)

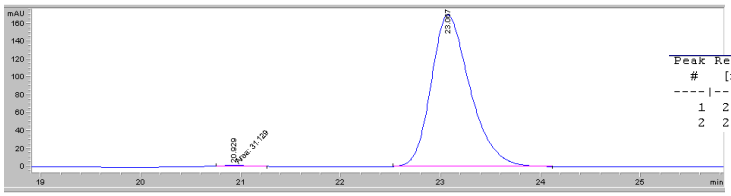
Chiral HPLC: (Daicel Chiralcel-IB column (25 cm) with guard, hexane:isopropanol = 98:2, 0.5 mL/min, room temperature, 210.8 nm): tR = 20.5 minutes (minor), 22.7 minutes (major), e.r. = 93:7 (Li), e.r. > 99:1 (Mg)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.485	BV	0.3725	6348.99463	254.99316	51.4036
2	22.715	VB	0.4419	6002.26514	211.01735	48.5964

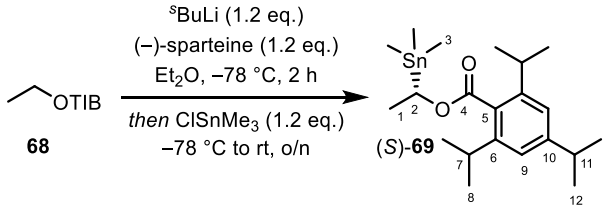


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.851	BB	0.3851	1203.91187	47.28028	6.8658
2	22.970	BB	0.4402	1.63309e4	566.62854	93.1342



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.929	MM	0.3508	31.12901	1.47888	0.6718
2	23.067	BB	0.4082	4602.38721	169.80510	99.3282

(*S*)-1-(Trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (*S*)-(**69**)



Prepared according to Aggarwal *et al.*[48]

[α]$^{22}_{D}$: + 37 ° (*c* 1.0, $CHCl_3$)

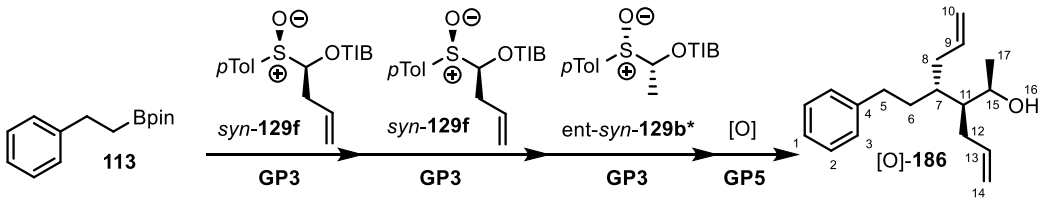
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (s, 2H, H-9), 5.05 (q, *J* = 7.7 Hz, 1H, H-2), 2.93-2.82 (m, 3H, H-7 and H-11), 1.60 (d, *J* = 7.7 Hz, 3H, H-1), 1.24 (d, *J* = 6.9 Hz, 18H, H-8 and H-11), 0.19 (s, 9H, H-3)

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4 (CO), 150.1 (C), 145.0 (2 × C) 130.9 (C), 120.9 (2 × CH), 67.2 (CH), 34.6 (CH), 31.5 (2 × CH), 24.5 (2 × CH_3), 24.3 (2 × CH_3), 24.1 (2 × CH_3), 19.4 (CH_3), –9.7 (3 × CH_3)

Data in accordance with that reported in the literature.[48]

(*R*)-**69** was prepared according to the same procedure but using (+)-sparteine.

(2*S*, 3*R*, 4*S*)-3-Allyl-4-phenethylhept-6-en-2-ol [O]-(173)

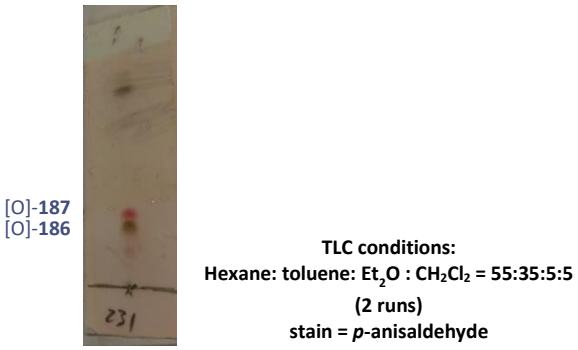


1st homologation: According to **GP3** using homoallylic sulfoxide *syn*-**129f** (485 mg, 1.10 mmol), phenylethyl pinacol boronic ester **113** (233 mg, 1.00 mmol) and ^{t}BuLi (1.7 M in pentane, 1.18 mL, 2.00 mmol). The solvent was removed under reduced pressure and the residue was suspended in pentane/Et_2O (95:5, *ca*. 20 mL). The suspension was filtered (~ 6 cm depth of wetted silica), the silica was washed (180 mL, Pentane:Et_2O = 95:5) and the solvent was removed under reduced pressure to give the crude homologated boronic ester.

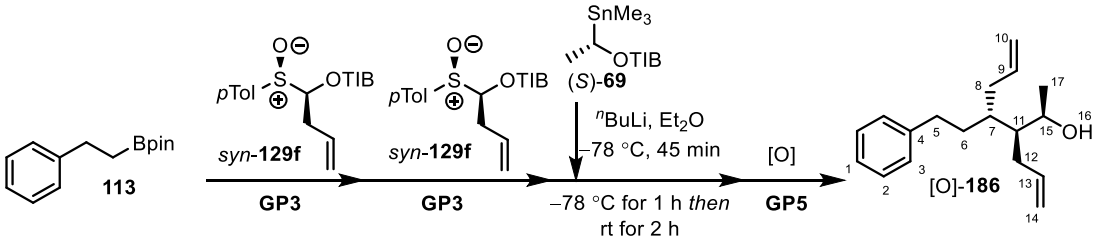
2nd homologation: The crude product from the first homologation was dissolved in toluene (4 mL) and transferred to an oven dried Schlenk tube. The solvent was removed under reduced pressure and the compound was dried on high vacuum for 1 h with stirring. The reaction was performed according to **GP3** using homoallylic sulfoxide *syn*-**129f** (485 mg, 1.10 mmol), the crude boronic ester obtained from the first homologation (assumed 1.00 mmol) and ^{t}BuLi (1.7 M in pentane, 1.18 mL, 2.00 mmol). The solvent was removed under reduced pressure and the residue was suspended in pentane/Et_2O (95:5, *ca*. 20 mL). The suspension was filtered (~ 6 cm depth of wetted silica), the silica was washed (180 mL, Pentane:Et_2O = 95:5) and the solvent was removed under reduced pressure to give the crude homologated boronic ester.

3rd homologation (with α-sulfinyl benzoate): The crude product from the second homologation was divided into three batches (3 mL of a 9 mL solution in toluene was transferred to an oven dried Schlenk tube). The solvent was removed under reduced pressure and the compound was dried on high vacuum for 1 h with stirring. The reaction was performed according to modified **GP3** using methyl sulfoxide *ent-syn*-**129b** (207 mg, 0.50 mmol), the crude boronic ester obtained from the second homologation (assumed 0.33 mmol), and ^{t}BuLi (1.7 M in pentane, 583 µL, 0.99 mmol). The solvent removed under reduced pressure and the residue was suspended in pentane/Et_2O (95:5, *ca*. 20 mL). The suspension was filtered (~ 6 cm depth of wetted silica), the silica was washed (180 mL, Pentane:Et_2O = 95:5) and the solvent was removed under reduced pressure to give

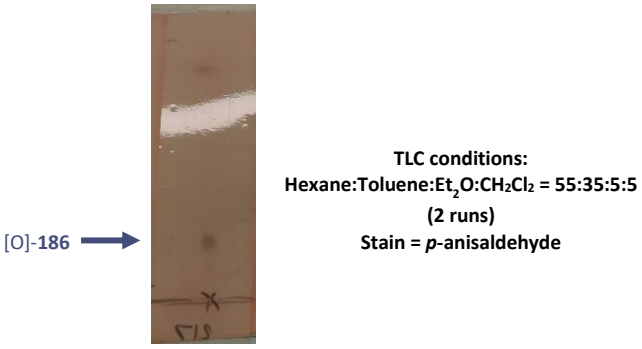
crude boronic ester. Oxidation of the crude boronic ester was performed according to **GP5** using $NaBO_3$•$4H_2O$ (508 mg, 3.30 mmol) for 3 h.



Purification by silica gel chromatography (Hexane:Toluene:Et_2O:CH_2Cl_2 = 100:0:0:0 → 58:35:5:2) gave [O]-**186** as a colourless oil (35 mg, 41% over 4 steps, d.r. >95:5).



3rd homologation (with stannane (*S*)-**69):** The crude product from the second homologation was divided into three batches (3 mL of a 9 mL solution in toluene was transferred to an oven dried Schlenk tube). The solvent was removed under reduced pressure and the compound was dried on high vacuum for 1 h with stirring. The reaction was performed according to S. Balieu *et al.*[70] using stannane (*S*)-**69** (198 mg, 0.45 mmol), the crude boronic ester obtained from the second homologation (assumed 0.33 mmol), and ^{n}BuLi (1.6 M in hexanes, 269 µL, 0.43 mmol) in Et_2O (2.5 mL). The reaction mixture was filtered through silica (~10 mm depth of wetted (Et_2O) silica, using a filter frit connected directly to an oven dried receiving vessel) to give a pale yellow solution. The silica was washed with Et_2O (reagent grade, 20 mL) and the solvent was removed under reduced pressure to give the crude boronic ester. Oxidation of the crude boronic ester was performed according to **GP5** using $NaBO_3$•$4H_2O$ (508 mg, 3.30 mmol) for 3 h.



Purification by silica gel chromatography (Hexane:Toluene:Et_2O:CH_2Cl_2 = 100:0:0:0 → 58:35:5:2) gave [O]-**186** as a colourless oil (44 mg, 52% over 4 steps, d.r. >95:5).

[α]$^{22}_D$: – 12 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.25 (m, 2H, H-2), 7.21–7.15 (m, 3H, H-1 and H-3), 5.83–5.71 (m, 2H, H-9 and H-13), 5.08–4.95 (m, 4H, H-10 and H-14), 3.71 (app. sext, *J* = 6.1 Hz, 1H, H-15), 2.67 (m, 1H, H-5a), 2.55 (m, 1H, H-5b), 2.25 (m , 1H, H-8a) 2.19-2.06 (m, 3H, H-8b and H-12), 1.82 (m, 1H, H-6a), 1.77 (m, 1H, H-7), 1.63-1.42 (m, 2H, H-11 and H-6b), 1.13 (d, *J* = 6.1 Hz, 3H, H-17) (*OH not observed*) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 142.9 (C), 139.1 (CH), 138.0 (CH), 128.6 (2 × CH), 128.5 (2 × CH), 125.9 (CH), 116.3 (CH_2), 115.7 (CH_2), 69.2 (CH), 49.4 (CH), 37.0 (CH), 36.7 (CH_2), 34.4 (CH_2), 32.8 (CH_2), 31.4 (CH_2), 21.8 (CH_3) ppm

IR (neat): 3397, 2920, 2851, 1455, 909 cm^{-1}

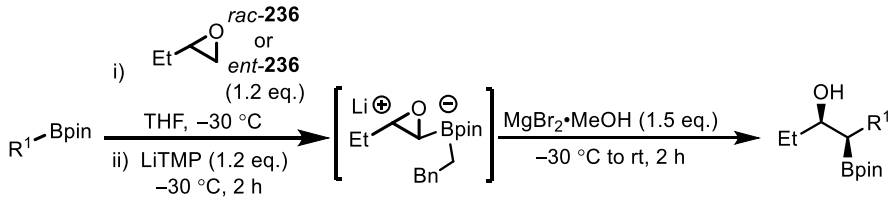
HRMS (ESI) calculated for $C_{18}H_{26}ONa$: 281.1876, found: 281.1865

R_f = 0.18 (Hexane/Toluene/Et_2O/CH_2Cl_2 = 55:35:5:5)

7.4. Lithiated Epoxides for the Introduction of Hydroxyl Groups into Assembly–Line Synthesis

7.4.1. *General Procedures*

General procedure 6 (**GP6**): Homologation of Boronic Esters with Lithiated Epoxides

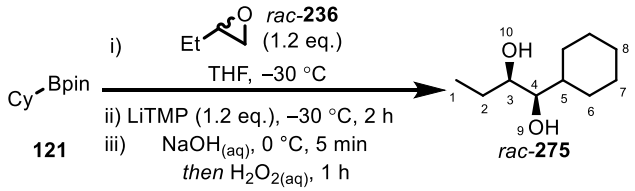


149 **273**

Freshly prepared LiTMP (0.58 M in THF, 1.2 eq.) was added dropwise (0.1 mL/min) to a solution of boronic ester (1.0 eq.) and 2-ethyl oxirane (**236**) (1.2 eq.) in THF (1 M w.r.t Bpin) at –30 °C. The reaction mixture was stirred for 2-5 h, at which point $MgBr_2$•MeOH (1.0 M, 1.5 eq.) was added dropwise. The reaction mixture was warmed to rt and stirred for an additional 2 h before dilution with EtOAc and sat. $NH_4Cl_{(aq)}$. The phases were separated and the aqueous phase was extracted with EtOAc (×3). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give the crude product, which was either purified by flash column chromatography or subject to silyl protection.

7.4.2. *Preparation of Individual Compounds*

***Syn*- 1-cyclohexylbutane-1,2-diol *rac*-(275)**



Freshly prepared LiTMP (0.58 M in THF, 2.07 mL, 1.20 mmol) was added dropwise (0.1 mL/min) to a solution of boronic ester **121** (210 mg, 1.00 mmol) and 2-ethyl oxirane *rac*-(**236**) (105 μL, 1.20 mmol) in THF (1.00 mL) at –30 °C. The reaction mixture was stirred for 2 h, at which point the reaction was poured onto 2 M $NaOH_{(aq)}$ (1 mL) at 0 °C. The reaction flask was washed with THF (2 × 1 mL) and the washings were added. The reaction mixture was stirred at 0 °C for 5 min, at which point 30% $H_2O_{2\,(aq)}$ (1 mL) was added dropwise. The reaction mixture was stirred for an additional 1 h before warming to rt. The reaction was diluted with 2 M $NaOH_{(aq)}$ (5 mL) and EtOAc (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with sat. $Na_2S_2O_{3\,(aq)}$ (5 mL), brine (5 mL), 3 M $HCl_{(aq)}$ (5 mL) and water (5 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give the crude product. Purification of the crude residue by flash column chromatography (Pentane:EtOAc = 100:0 → 80:20) gave *rac*-**275** (119 mg, 69%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.56 (td, J_1 = 8.0 Hz, J_2 = 4.6 Hz, 1H, H-3), 3.16 (dd, J_1 = 5.5 Hz, J_2 = 4.6 Hz, 1H, H-4), 1.86-1.72 (m, 4H, H-Cy, H-9 and H-10), 1.70-1.62 (m, 2H, H-Cy), 1.61-1.40 (m, 3H, H-Cy and H-2), 1.32-1.04 (m, 6H, H-Cy), 0.97 (t, J = 7.5 Hz, 3H, H-1) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 78.1 (CH), 72.9 (CH), 40.3 (CH), 30.0 (CH_2), 27.9 (CH_2), 27.0 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 26.2 (CH_2), 10.2 (CH_3) ppm

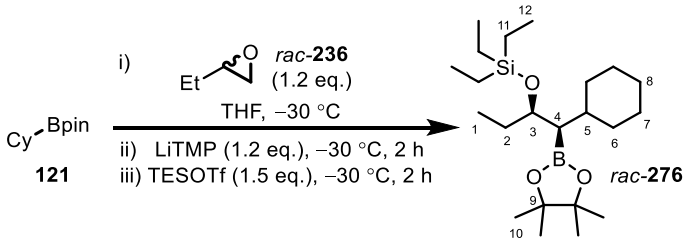
IR (neat): 3372 (br.), 2925, 2802, 1450, 970, 408 cm^{-1}

HRMS (ESI) calculated for: $C_{10}H_{20}O_2Na$: 195.1355, found 195.1361

M.P. 58–60 ºC (EtOAc)

R_f = 0.28 (Pentane:EtOAc = 60:40)

Syn-1-cyclohexyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-yl)oxy)triethylsilane _rac_-(276)



Freshly prepared LiTMP (0.58 M in THF, 2.07 mL, 1.20 mmol) was added dropwise (0.1 mL/min) to a solution of boronic ester **121** (210 mg, 1.00 mmol) and 2-ethyl oxirane *rac*-(**236**) (105 μL, 1.20 mmol) in THF (1.00 mL) at –30 °C. The reaction mixture was stirred for 2 h, at which point TESOTf (340 μL, 1.50 mmol) was added dropwise. The reaction mixture was stirred at –30 °C for 1 h, warmed to rt and stirred for an additional 1 h before dilution with EtOAc (5 mL) and water (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give the crude product. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 80:20) gave *rac*-**276** (183 mg, 46%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (m, 1H, H-3), 1.84 (br. d, *J* = 13.3 Hz, 1H, H-Cy), 1.75 (br. d, *J* = 13.3 Hz, 1H, H-Cy), 1.72-1.47 (m, 6H, H-Cy and H-2), 1.29-1.06 (m, 4H, H-Cy and H-4), 1.23 (s, 6H, H-10a), 1.22 (s, 6H, H-10b), 0.96 (t, *J* = 7.8 Hz, 9H, H-12), 0.94-0.81 (m, 2H, H-Cy), 0.84 (t, *J* = 7.3 Hz, 3H, H-1), 0.57 (q, *J* = 7.8 Hz, 6H, H-11) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 82.7 (2 × C), 73.5 (CH), 36.1 (CH), 33.4 (CH_2), 33.3 (CH_2), 29.9 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 25.5 (2 × CH_3), 24.7 (2 × CH_3), 10.1 (CH_3), 7.2 (3 × CH_3), 5.5 (3 × CH_2) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

^{11}B NMR (96 MHz): 32.6 ppm

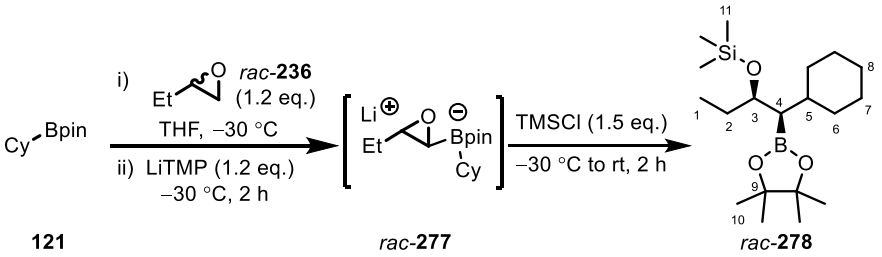
IR (neat): 2926, 2874, 1317, 1145, 1009, 721 cm^{-1}

HRMS (ESI) calculated for: $C_{22}H_{45}BO_3SiNa$: 419.3128, found 419.3138

R_f = 0.40 (Pentane:CH_2Cl_2 = 60:40)

Note: Compound is prone to decomposition and should be stored in the freezer

Syn-1-cyclohexyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-yl)oxy)trimethylsilane *rac*-(**278**)



Freshly prepared LiTMP (0.58 M in THF, 2.07 mL, 1.20 mmol) was added dropwise (0.1 mL/min) to a solution of boronic ester **121** (210 mg, 1.00 mmol) and 2-ethyl oxirane *rac*-(**236**) (105 μL, 1.20 mmol) in THF (1.00 mL) at –30 °C. The reaction mixture was stirred for 2 h, at which point TMSCl (191 μL, 1.50 mmol) was added dropwise. The reaction mixture was warmed to rt and stirred for an additional 2 h before dilution with EtOAc (5 mL) and water (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give the crude product. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 60:40) gave *rac*-**278** (156 mg, 44%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (app. q, *J* = 5.3 Hz, 1H, H-3), 1.83-1.38 (m, 9H, H-Cy and H-2), 1.26-0.87 (m, 17H, H-Cy, H-4 and H-10), 0.83 (t, *J* = 7.2 Hz, 3H, H-1), 0.09 (s, 9H, H-11) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 82.8 (2 × C), 73.3 (CH), 36.3 (CH), 33.6 (CH_2), 32.8 (CH_2), 29.3 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 25.5 (2 × CH_3), 24.8 (2 × CH_3), 9.4 (CH_3), 0.8 (3 × CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

^{11}B NMR (96 MHz): 32.8 ppm

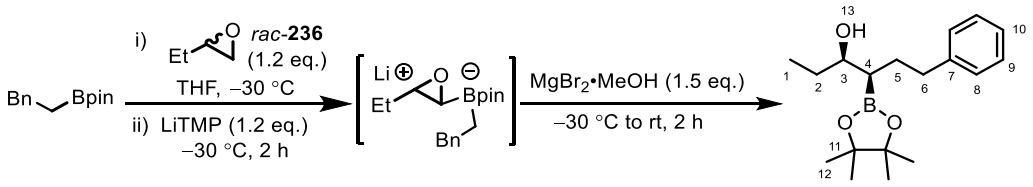
IR (neat): 2922, 1317, 1248, 1146, 836 cm^{-1}

HRMS (ESI) calculated for: $C_{19}H_{39}BO_3SiNa$:377.2658, found 377.2663

R_f = 0.20 (Pentane:CH_2Cl_2 = 60:40)

Note: Compound is prone to decomposition and should be stored in the freezer

Syn-6-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-ol *rac*-(**279**)



113 *rac*-**271** *rac*-**279**

According to **GP6** using LiTMP (2.07 mL, 1.20 mmol), boronic ester **113** (233 mg, 1.00 mmol), 2-ethyl oxirane *rac*-(**236**) (106 μL, 1.20 mmol) in THF (1.00 mL) for 2 h then $MgBr_2$•MeOH (1.0 M, 1.50 mL, 1.50 mmol). Purification of the crude residue by flash column chromatography (Pentane:EtOAc = 100:0 → 90:10) gave *rac*-**279** (208 mg, 69%) as a colourless oil, which crystallised into a white solid on standing.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.24 (m, 2H, H-9), 7.22-7.14 (m, 3H, H-8 and H-10), 3.58 (m, 1H, H-3), 2.69-2.59 (m, 2H, H-6), 2.06 (d, *J* = 8.0 Hz, 1H, H-13), 1.91-1.74 (m, 2H, H-5), 1.57-1.40 (m, 2H, H-2), 1.28 (s, 12H, H-12), 1.25 (m, 1H, H-4), 0.95 (t, *J* = 7.4 Hz, 3H, H-1) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 142.8 (C), 128.5 (2 × CH), 128.4 (2 × CH), 125.8 (CH), 83.6 (2 × C), 75.3 (CH), 35.6 (CH_2), 30.8 (CH_2), 30.7 (CH_2), 25.0 (2 × CH_3), 24.9 (2 × CH_3), 10.6 (CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

^{11}B NMR (96 MHz): 33.0 ppm

IR (neat): 3510 (br.), 2977, 2922, 1312, 1139, 774, 702 cm^{-1}

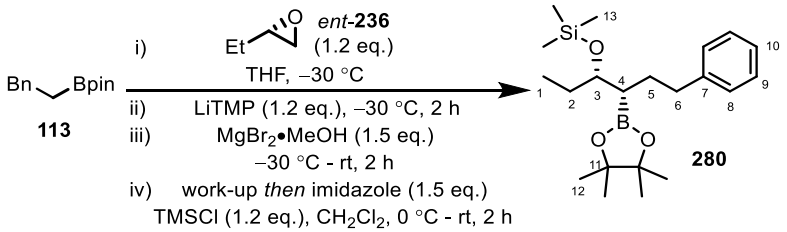
HRMS (ESI) calculated for $C_{18}H_{29}BO_3Na$: 327.2105, found 327.2118

M.P. 38–40 ºC (EtOAc)

R_f = 0.15 (Pentane:EtOAc = 90:10)

Note: Compound is prone to decomposition and should be stored in the freezer

Trimethyl(((3*S*,4*S*)-6-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl)oxy)silane (**280**)



According to **GP6** using LiTMP (2.07 mL, 1.20 mmol), boronic ester **113** (233 mg, 1.00 mmol), (*S*)-2-ethyl oxirane *ent*-(**236)** (106 µL, 1.20 mmol) in THF (1.00 mL) for 2 h then $MgBr_2$•MeOH (1.0 M, 1.50 mL, 1.50 mmol). The crude product was dissolved in CH_2Cl_2 (10.0 mL) and imidazole (102 mg, 1.50 mmol) was added. The solution was cooled to 0 °C and TMSCl (164 µL, 1.20 mmol) was added dropwise, after which the reaction mixture was warmed to rt and stirred for 2 h. The reaction mixture was diluted with H_2O (10 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Hexane:EtOAc = 100:0 → 97:3) gave **280** (232 mg, 62%) as a colourless oil.

$[\alpha]^{22}_D$: – 8 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.23 (m, 2H, H-9), 7.21-7.12 (m, 3H, H-8 and H-10), 3.72 (dt, J_1 = 7.1 Hz, J_2 = 4.5 Hz, 1H, H-3), 2.69 (ddd, J_1 = 13.7 Hz, J_2 = 8.7 Hz, J_3 = 5.1 Hz, 1H, H-6a), 2.52 (ddd, J_1 = 13.7 Hz, J_2 = 9.7 Hz, J_3 = 7.0 Hz, 1H, H-6b), 1.81 (m, 1H, H-5a), 1.71 (m, 1H, H-5b), 1.60-1.41 (m, 2H, H-2), 1.26 (s, 6H, H-12a), 1.25 (s, 6H, H-12b), 1.21 (m, 1H, H-4), 0.83 (t, *J* = 7.2 Hz, 3H, H-1), 0.07 (s, 9H, H-13) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 143.2 (C), 128.7 (2 × CH), 128.3 (2 × CH), 125.6 (CH), 83.0 (2 × C), 76.1 (CH), 36.1 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 25.3 (2 × CH_3), 24.8 (2 × CH_3), 10.5 (CH_3), 0.7 (3 × CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

^{11}B NMR (96 MHz): 34.2 ppm

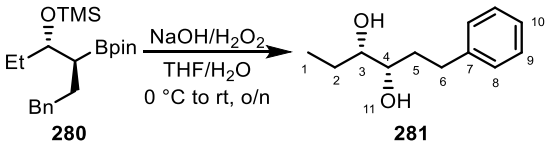
IR (neat): 2976, 2932, 1249, 1145, 837, 698 cm^{-1}

HRMS (ESI) calculated for $C_{21}H_{37}BO_3SiNa$: 399.2501, found 399.2502

R_f = 0.55 (Pentane:EtOAc = 90:10)

Note: Compound is prone to decomposition and should be stored in the freezer

(3*S*,4*S*)-1-Phenylhexane-3,4-diol (281)



280 **281**

To a solution of boronic ester **280** (11.3 mg, 0.03 mmol) in THF (1.00 mL) at 0 °C was added 2 M $NaOH_{(aq)}/H_2O_2$ (2:1 v/v, 500 µL) dropwise. The reaction mixture was warmed to rt and stirred vigorously for 2 h. The reaction mixture was diluted with H_2O (5 mL) and EtOAc (5 mL) the phases were separated. The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (CH_2Cl_2:EtOAc = 100:0 → 80:20) gave **281** (3.3 mg, 57%) as a colourless oil.

$[\alpha]^{22}_D$: – 16 ° (*c* 0.6, $CHCl_3$)

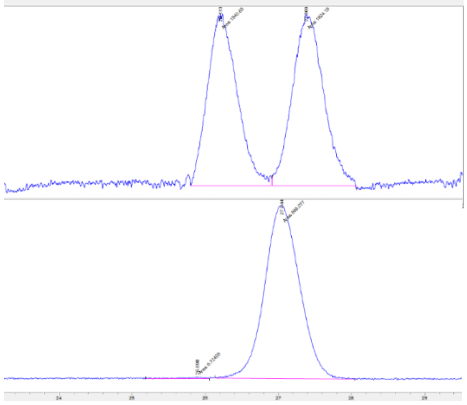
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2H, H-8 or H-9), 7.23-7.16 (m, 3H, H-8 or H-9 and H-10), 3.46 (m, 1H, H-3 or H-4), 3.38 (m, 1H, H-3 or H-4), 2.85 (ddd, J_1 = 13.8 Hz, J_2 = 9.0 Hz, J_3 = 6.1 Hz, 1H, H-6a), 2.69 (ddd, J_1 = 13.8 Hz, J_2 = 9.2 Hz, J_3 = 7.2 Hz, 1H, H-6b), 2.09 (br. s, 1H, H-11 or H-12), 1.96 (br. s, 1H, H-11 or H-12), 1.87-1.74 (m, 2H, H-5), 1.57 (m, 1H, H-2a), 1.44 (ddq, J_1 = 14.0 Hz, J_2 = 8.3 Hz, J_3 = 7.5 Hz, 1H, H-2b), 0.96 (t, J = 7.5 Hz, 3H, H-1) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 141.9 (C), 128.4 (4 × CH), 125.9 (CH), 76.0 (CH), 73.5 (CH), 35.3 (CH_2), 32.0 (CH_2), 26.5 (CH_2), 9.9 (CH_3) ppm

Spectral data in accordance with lit.[119]

rac-**148** was prepared using the same procedure from *rac*-**280**.

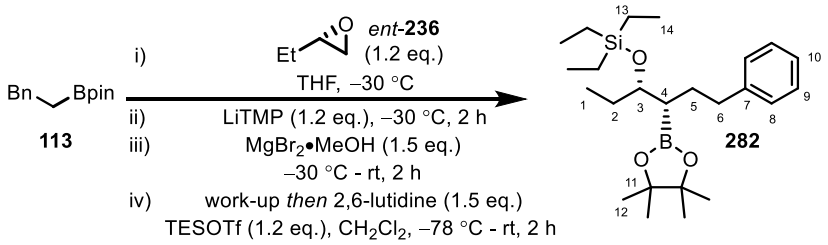
Chiral HPLC: (Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 97:3, 1.0 mL/min, room temperature, 254.1 nm): tR = 25.9 minutes (min), 27.0 minutes (maj), e.r. >99:1



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	26.113	MM	1540.7	51	0.5037	48.680	0.744
2	27.369	MM	1624.2	51	0.531	51.320	0.791

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	25.89	MM	6.7	3E-1	0.3684	0.771	2.989
2	27.044	MM	865.1	25.9	0.5561	99.229	0.919

Triethyl(((3*S*,4*S*)-6-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl)oxy)silane (**282**)



According to **GP6** using LiTMP (2.07 mL, 1.20 mmol), boronic ester **113** (233 mg, 1.00 mmol), (*S*)-2-ethyl oxirane *ent*-(**236**) (106 µL, 1.20 mmol) in THF (1.00 mL) for 2 h then $MgBr_2$•MeOH (1.0 M, 1.50 mL, 1.50 mmol). The crude product was dissolved in CH_2Cl_2 (10.0 mL) and 2,6-lutidine (175 µL, 1.50 mmol) was added. The solution was cooled to –78 °C and TESOTf (272 µL, 1.20 mmol) was added dropwise and the reaction mixture was stirred for 2 h before warming to rt and stirring o/n. The reaction mixture was diluted with H_2O (10 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Hexane:CH_2Cl_2 = 100:0 → 80:20) gave **282** (279 mg, 67%) as a colourless oil.

$[\alpha]^{22}_D$: – 18 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.23 (m, 2H, H-9), 7.21-7.12 (m, 3H, H-8 and H-10), 3.73 (td, J_1 = 6.2 Hz, J_2 = 3.0 Hz, 1H, H-3), 2.69 (ddd, J_1 = 13.3 Hz, J_2 = 9.2 Hz, J_3 = 5.2 Hz, 1H, H-6a), 2.53 (ddd, J_1 = 13.3 Hz, J_2 = 10.0 Hz, J_3 = 6.7 Hz, 1H, H-6b), 1.84 (m, 1H, H-5a), 1.75 (m, 1H, H-5b), 1.51 (app. br. pent., J = 7.2 Hz, 2H, H-2), 1.25 (s, 6H, H-12a), 1.24 (s, 6H, H-12b), 1.22 (m, 1H, H-4), 0.95 (t, J = 7.9 Hz, 9H, H-14), 0.83 (t, J = 7.2 Hz, 3H, H-1), 0.56 (q, J = 7.9 Hz, 6H, H-13) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 143.4 (C), 128.6 (2 × CH), 128.3 (2 × CH), 125.6 (CH), 83.0 (2 × C), 76.2 (CH), 36.2 (CH_2), 31.8 (CH), 29.3 (CH_2), 29.0 (CH_2), 25.4 (2 × CH_3), 24.7 (2 × CH_3), 11.0 (CH_3), 7.2 (3 × CH_3), 5.3 (3 × CH_2) ppm

^{11}B NMR (96 MHz): 32.0 ppm

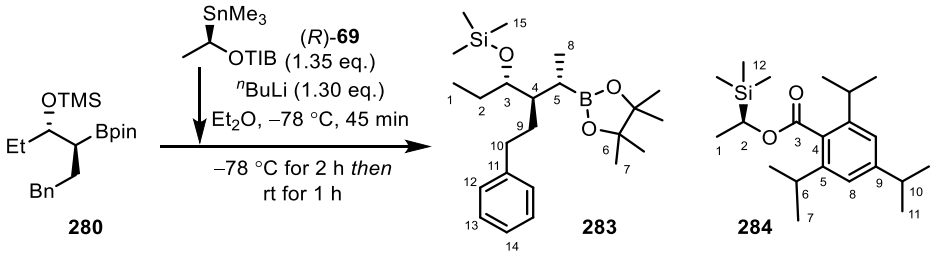
IR (neat): 2953, 2878, 1316, 1008, 696 cm^{-1}

HRMS (ESI) calculated for $C_{24}H_{43}BO_3SiNa$: 418.3079, found 418.3088

R_f = 0.46 (Hexane:CH_2Cl_2 = 50:50)

Note: Compound is prone to decomposition and should be stored in the freezer

Trimethyl(((3*S*,4*R*,5*S*)-4-phenethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl)oxy)silane (283) and (*R*)-1-(trimethylsilyl)ethyl 2,4,6-triisopropylbenzoate (284)



According to S. Balieu *et al.*[70] using stannane (*R*)-**69** (297 mg, 0.68 mmol), boronic ester **280** (188 mg, 0.50 mmol), and ^{n}BuLi (1.6 M in hexanes, 408 μL, 0.65 mmol) in Et_2O (3.75 mL). The reaction mixture was filtered through silica (~10 mm depth of wetted (Et_2O) silica, using a filter frit connected directly to an oven dried receiving vessel) to give a pale yellow solution. The silica was washed with Et_2O (reagent grade, 20 mL) and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Hexane:Toluene = 100:0 → 70:30) gave silane **284** (44 mg, 31%) as a pale yellow oil and boronic ester **283** (66 mg, 33%) as a colourless oil.

Boronic ester **283**

$[\alpha]^{22}_D$: – 16 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.23 (m, 2H, H-13), 7.21-7.12 (m, 3H, H-12 and H-14), 3.72 (dt, J_1 = 7.8 Hz, J_2 = 4.5 Hz, 1H, H-3), 2.73-2.58 (m, 2H, H-10), 1.73 (ddt, J_1 = 13.2 Hz, J_2 = 10.7 Hz, J_3 = 5.5 Hz, 1H, H-9a), 1.65 (app. pent, J = 5.5 Hz, 1H, H-4), 1.60-1.36 (m, 3H, H-2 and H-9b), 1.24 (s, 6H, H-7a), 1.22 (s, 6H, H-7b), 1.20 (m, 1H, H-5), 0.96 (d, J = 7.4 Hz, 3H, H-8), 0.87 (t, J = 7.0 Hz, 3H, H-1), 0.11 (s, 9H, H-15) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 143.4 (C), 128.3 (2 × CH), 128.2 (2 × CH), 125.4 (CH), 82.3 (2 × C), 75.8 (CH), 45.8 (CH), 35.2 (CH_2), 31.4 (CH_2), 25.7 (CH_2), 25.0 (2 × CH_3), 24.7 (2 × CH_3), 18.0 (CH), 13.7 (CH_3), 10.3 (CH_3), 0.7 (3 × CH_3) ppm

^{11}B NMR (96 MHz): 33.9 ppm

IR (neat): 2959, 2875, 1249, 1144, 1012, 837, 697 cm^{-1}

HRMS (ESI) calculated for $C_{23}H_{41}BO_3SiNa$: 427.2815, found 427.2818

R_f = 0.11 (Hexane:Toluene = 70:30)

Silane **284**

$[\alpha]^{22}_{D}$: + 8 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (s, 2H, H-8), 5.03 (q, *J* = 7.3 Hz, 1H, H-2), 2.93-2.82 (m, 3H, H-6 and H-10), 1.38 (d, *J* = 7.3 Hz, 3H, H-1), 1.25 (d, *J* = 6.9 Hz, 6H, H-7 or H-11), 1.24 (d, *J* = 6.9 Hz, 6H, H-7a or H-11), 1.23 (d, *J* = 6.9 Hz, 6H, H-7 or H-11), 0.08 (s, 9H, H-12) ppm

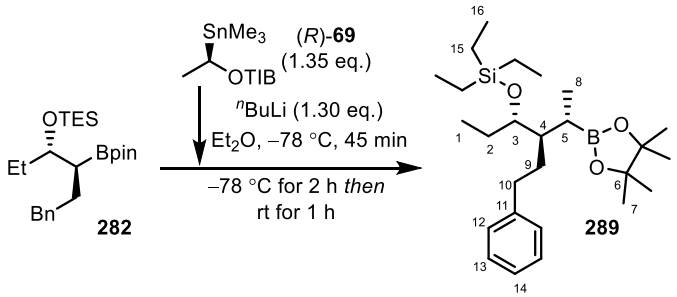
^{13}C NMR (101 MHz, $CDCl_3$): 171.2 (CO), 149.7 (C), 144.6 (2 × C), 131.1 (C), 120.7 (2 × CH), 65.4 (CH), 34.3 (CH), 31.2 (2 × CH), 24.5 (2 × CH_3), 24.0 (4 × CH_3), 15.8 (CH_3), –3.9 (3 × CH_3) ppm

IR (neat): 2960, 2870, 1718, 1250, 1069, 838, 772 cm^{-1}

HRMS (ESI) calculated for $C_{21}H_{36}O_2SiNa$: 371.2377, found 371.2380

R_f = 0.30 (Hexane:Toluene = 70:30)

Triethyl(((3*S*,4*R*,5*S*)-4-phenethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl)oxy)silane (**289**)



According to S. Balieu *et al.*[70] using stannane (*R*)-**69** (149 mg, 0.34 mmol), boronic ester **282** (105 mg, 0.25 mmol), and ^{n}BuLi (1.6 M in hexanes, 204 µL, 0.33 mmol) in Et_2O (1.80 mL). The reaction mixture was filtered through silica (~10 mm depth of wetted (Et_2O) silica, using a filter frit connected directly to an oven dried receiving vessel) to give a pale yellow solution. The silica was washed with Et_2O (reagent grade, 20 mL) and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:Toluene = 100:0 → 80:20) gave boronic ester **289** (85 mg, 76%) as a colourless oil.

$[\alpha]^{22}_{D}$: – 11 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.23 (m, 2H, H-13), 7.21-7.12 (m, 3H, H-12 and H-14), 3.73 (dt, J_1 = 8.0 Hz, J_2 = 4.1 Hz, 1H, H-3), 2.73-2.59 (m, 2H, H-10), 1.82 (ddt, J_1 = 13.8 Hz, J_2 = 10.8 Hz, J_3 = 6.4 Hz, 1H, H-9a), 1.65 (dddd, J_1 = 6.4 Hz, J_2 = 6.2 Hz, J_3 = 4.4 Hz, J_4 = 4.1 Hz, 1H, H-4), 1.60-1.33 (m, 3H, H-2 and H-9b), 1.24 (s, 6H, H-7a), 1.23 (s, 6H, H-7b), 1.16 (m, 1H, H-5), 1.00-0.98 (m, 3H, H-8), 0.97 (t, *J* = 7.9 Hz, 9H, H-16), 0.89 (t, *J* = 7.3 Hz, 3H, H-1), 0.62 (q, *J* = 7.9 Hz, 6H, H-15) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 143.8 (C), 128.5 (2 × CH), 128.3 (2 × CH), 125.5 (CH), 82.9 (2 × C), 76.1 (CH), 45.6 (CH), 35.6 (CH_2), 31.8 (CH_2), 25.6 (CH_2), 25.0 (4 × CH_3), 18.7 (CH), 14.5 (CH_3), 10.9 (CH_3), 7.3 (3 × CH_3), 5.5 (3 × CH_2) ppm

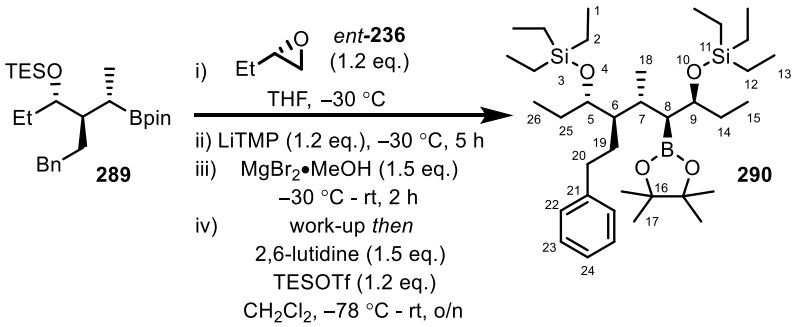
^{11}B NMR (96 MHz): 34.0 ppm

IR (neat): 2956, 2876, 1378, 1414, 1143, 1005, 738, 698 cm^{-1}

HRMS (ESI) calculated for $C_{26}H_{47}BO_3SiNa$: 469.3285, found 469.3277

R_f = 0.11 (Pentane:Toluene = 70:30)

(5*S*,6*R*,7*R*,8*S*,9*S*)-3,3,5,9,11,11-hexaethyl-7-methyl-6-phenethyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4,10-dioxa-3,11-disilatridecane (**290**)



According to **GP6** using LiTMP (502 µL, 0.30 mmol), boronic ester **289** (112 mg, 0.25 mmol), (*S*)-2-ethyl oxirane *ent*-(**236**) (27 µL, 0.30 mmol) in THF (250 µL) for 5 h then $MgBr_2$•MeOH (1.0 M, 375 µL, 0.38 mmol). The crude product was dissolved in CH_2Cl_2 (2.50 mL) and 2,6-lutidine (44 µL, 0.38 mmol) was added. The solution was cooled to –78 °C and TESOTf (68 µL, 0.30 mmol) was added dropwise and the reaction mixture was stirred for 2 h before warming to rt. The reaction mixture was diluted with H_2O (5 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 90:10) gave boronic ester **290** (66 mg, 42%) as a colourless oil. Further elution (Pentane:CH_2Cl_2 = 90:10 → 75:25) gave recovered starting material **289** (24 mg, 22%) as a colourless oil.

$[\alpha]^{22}_D$: – 25 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.24 (m, 2H, H-23), 7.21-7.13 (m, 3H, H-22 and H-24), 3.81 (m, 1H, H-9), 3.76 (m, 1H, H-5), 2.82-2.61 (m, 2H, H-20), 1.92 (m, 1H, H-6), 1.76 (m, 1H, H-14a), 1.69-1.41 (m, 7H, H-7, H-8, H-14b, H-19, H-25), 1.21 (s, 12H, H-17), 1.02-0.94 (m, 21H, H-1, H-13 and H-18), 0.90 (t, *J* = 7.4 Hz, 3H, H-26), 0.88 (t, *J* = 7.6 Hz, 3H, H-15), 0.62 (q, *J* = 7.9 Hz, 6H, H-2 or H-12), 0.59 (q, *J* = 7.7 Hz, 6H, H-2 or H-12) ppm

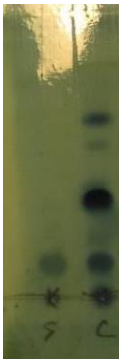
^{13}C NMR (101 MHz, $CDCl_3$): 143.4 (C), 128.4 (4 × CH), 125.5 (CH), 82.6 (2 × C), 75.2 (CH), 74.9 (CH), 47.6 (CH), 35.5 (CH_2), 35.3 (CH), 33.2 (CH), 32.4 (CH_2), 31.2 (CH_2), 26.7 (CH_2), 25.6 (2 × CH_3), 24.9 (2 × CH_3), 15.3 (CH_3), 11.2 (CH_3), 10.4 (CH_3), 7.3 (3 × CH_3), 7.2 (3 × CH_3), 5.8 (3 × CH_2), 5.6 (3 × CH_2) ppm

^{11}B NMR (96 MHz): 33.8 ppm

IR (neat): 2957, 2876, 1459, 1311, 1214, 1005, 752, 697 cm^{-1}

HRMS (ESI) calculated for $C_{36}H_{69}BO_4Si_2Na$: 655.4727, found 655.4716

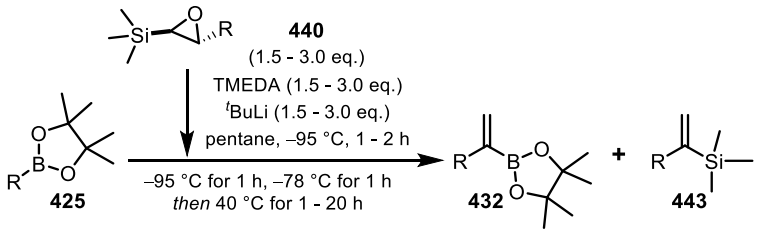
R_f = 0.33 (Pentane:CH_2Cl_2 = 85:15)



7.5. Vinylidene Homologation of Boronic Esters and its Application to the Synthesis and Structural Revision of Machillene

7.5.1. *General Procedures*

General Procedure 7 (**GP7**)

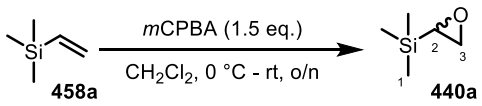


To a solution of TMEDA and epoxysilane **440** in pentane at –95 °C (liquid N_2/MeOH) was added ^{t}BuLi (1.7 M in pentane) dropwise (0.2 mL/min). The reaction mixture was stirred for 1-2 h, after which a solution of boronic ester in the specified solvent was added dropwise. The reaction mixture was stirred for 1 h, at which point the cooling bath was removed and quickly replaced with a –78 °C bath (dry ice/acetone) and stirred for an additional 1 h. The cooling bath was removed and the reaction vessel was warmed to rt, at which point it was placed in a 40 °C oil bath and stirred for the specified time (with the exception of substrate **1j**, for which the reaction mixture was stirred at rt for 1 h before heating at 40 °C for the specified time). The reaction was cooled to rt and diluted with sat. $NH_4Cl_{(aq)}$. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (× 3). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography gave the vinyl boronic ester product and/or vinyl silane product.

7.5.2. *Preparation of Individual Compounds*

The following compounds were prepared by the Aggarwal group according to literature procedures as part of the Aggarwal boronic ester database[‡]: adamantyl boronic ester **425c**,[201] nitrile boronic ester **425d**,[44] azidyl boronic ester **425e**, [202] cyclobutyl boronic ester **425f**,[203] azetidiny boronic ester **425g**,[204] cyclopropyl boronic ester **425h**,[205] menthyl boronic ester **425i**,[206] cholesteryl boronic ester **425j**,[207] *p*-methoxyphenyl boronic ester **425n**,[208] indolyl boronic ester **425o**,[209] *p*-chlorophenyl boronic ester **425p**,[210] styrenyl boronic ester **425s.**[211]

Trimethyl(oxiran-2-yl)silane (**440a**)



To a solution of vinyltrimethylsilane (**458a**) (7.32 mL, 50.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added a solution of *m*CPBA (16.8 g, 75.0 mmol) in CH_2Cl_2 (100 mL). The reaction mixture was allowed to warm to rt and stirred vigorously overnight. The reaction was quenched with sat. $NaHCO_{3(aq)}$ (50 mL) and the phases were separated. The organic layer was washed with sat. $NaHCO_{3(aq)}$ (5 × 50 mL), dried (Na_2SO_4), filtered and carefully concentrated (~7 mL) *in vacuo*. The crude product was subject to fractional distillation (3rd fraction, b.p. 109-110 °C) at atmospheric pressure to give epoxysilane **440a** (3.40 g, 60%) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (dd, J_1 = 5.9 Hz, J_2 = 5.6 Hz, 1H, H-3a), 2.56 (dd, J_1 = 5.9 Hz, J_2 = 4.1 Hz, 1H, H-3b), 2.20 (dd, J_1 = 5.6 Hz, J_2 = 4.1 Hz, 1H, H-2), 0.07 (s, 9H, H-1) ppm

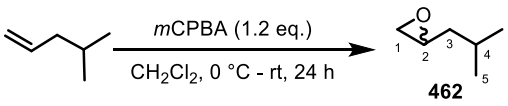
^{13}C NMR (101 MHz, $CDCl_3$): 44.7 (CH_2), 44.3 (CH), –3.7 (3 × CH_3) ppm

B.P. 109-110 °C

Data in accordance with that reported in the literature.[212]

Note: Fraction 1 - b.p. 40-41 °C - CH_2Cl_2 / Fraction 2 - b.p. 80-109 °C - CH_2Cl_2/Product (1:1)

2-isobutyloxirane (**462**)



To a solution of 4-methylpent-1-ene (1.26 mL, 10.0 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added a solution of *m*CPBA (2.68 g, 12.0 mmol) in CH_2Cl_2 (45 mL). The reaction mixture was allowed to warm to rt and stirred vigorously for 20 h. The reaction was quenched with sat. $NaHCO_{3\ (aq)}$ (20 mL) and the phases were separated. The organic layer was washed with sat. $NaHCO_{3(aq)}$ (5 × 20 mL), dried (Na_2SO_4), filtered and the volatiles were removed by distillation (95 °C) to give epoxide **462** (701 mg, 78% containing *ca.* 8% CH_2Cl_2 impurity) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.93 (dddd, J_1 = 6.6 Hz, J_2 = 5.3 Hz, J_3 = 4.0 Hz, J_4 = 2.7 Hz, 1H, H-2), 2.76 (ddd, J_1 = 5.1 Hz, J_2 = 4.0 Hz, J_3 = 0.5 Hz, 1H, H-1a), 2.44 (dd, J_1 = 5.1 Hz, J_2 = 2.7 Hz, 1H, H-1b), 1.84 (app. nonet, J = 6.7 Hz, 1H, H-4), 1.49-1.32 (m, 2H, H-3), 0.98 (d, J = 6.7 Hz, 3H, H-5a), 0.97 (d, J = 6.7 Hz, 3H, H-5b) ppm

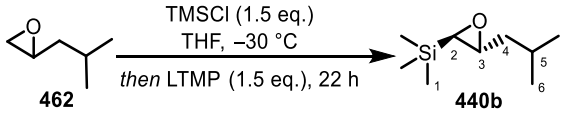
^{13}C NMR (101 MHz, $CDCl_3$): 51.4 (CH), 47.3 (CH_2), 41.8 (CH_2), 26.6 (CH), 23.1 (CH_3), 22.6 (CH_3) ppm

IR (neat): 2958, 2925, 1467, 1259, 1057, 841, 810 cm^{-1}

HRMS (APCI) calculated for $C_6H_{13}O$: 101.0961, found 101.0955

R_f = 0.28 (Pentane:CH_2Cl_2 = 70:30)

(*trans*-3-Isobutyloxiran-2-yl)trimethylsilane (**440b**)



To a solution of 2,2,6,6-tetramethylpiperidine (1.52 mL, 9.00 mmol) in THF (6.90 mL) at –30 °C was added ^{n}BuLi (1.53 M in hexanes, 5.88 mL, 9.00 mmol) dropwise (1 mL/min) and the resulting mixture was warmed to rt and stirred for 20 min. The freshly prepared LTMP (0.63 M in THF, 14.3 mL, 9.00 mmol) was added dropwise (2 mL/min) to a solution of epoxide **462** (540 mg, 6.00 mmol) and chlorotrimethylsilane (1.14 mL, 9.00 mmol) in THF (6.00 mL) at –30 °C. The resulting mixture was stirred for 22 h and quenched with sat. $NH_4Cl_{(aq)}$ (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL) and the combined extracts were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Petroleum ether 40-60: CH_2Cl_2 = 75:25) gave epoxysilane **440b** (205 mg, 20%) as an orange liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.93 (ddd, J_1 = 6.1 Hz, J_2 = 5.5 Hz, J_3 = 3.6 Hz, 1H, H-3), 1.94 (d, J = 3.6 Hz, 1H, H-2), 1.84 (app. nonet, J = 6.9 Hz, 1H, H-5), 1.56 (m, 1H, H-4a), 1.36 (ddd, J_1 = 13.4 Hz, J_2 = 6.7 Hz, J_3 = 5.5 Hz, 1H, H-4b), 0.98 (d, J = 6.7 Hz, 3H, H-6a), 0.96 (d, J = 6.7 Hz, 3H, H-6b), 0.06 (s, 9H, H-1) ppm

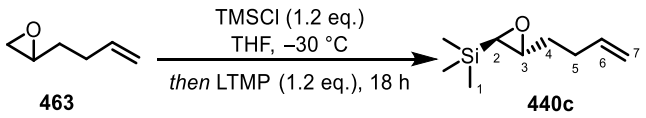
^{13}C NMR (101 MHz, $CDCl_3$): 55.2 (CH), 51.9 (CH), 43.4 (CH_2), 26.9 (CH), 23.2 (CH_3), 22.7 (CH_3), –3.5 (3 × CH_3) ppm

IR (neat): 2955, 2922, 146, 1250, 1055, 851cm^{-1}

HRMS (APCI) calculated for $C_9H_{21}OSi$: 173.1356, found 173.1349

R_f = 0.38 (Pentane:CH_2Cl_2 = 70:30)

trans-3-(But-3-en-1-yl)oxiran-2-yl)trimethylsilane (**440c**)



To a solution of 2,2,6,6-tetramethylpiperidine (1.01 mL, 6.00 mmol) in THF (4.60 mL) at –30 °C was added ^{n}BuLi (1.53 M in hexanes, 3.92 mL, 6.00 mmol) dropwise (1 mL/min) and the resulting mixture was warmed to rt and stirred for 20 min. The freshly prepared LTMP (0.63 M in THF, 9.53 mL, 6.00 mmol) was added dropwise (2 mL/min) to a solution of epoxide **463** (564 µL, 5.00 mmol) and chlorotrimethylsilane (762 µL, 6.00 mmol) in THF (5.00 mL) at –30 °C. The resulting mixture was stirred for 18 h and quenched with sat. $NH_4Cl_{(aq)}$ (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL) and the combined extracts were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Petroleum ether 40-60: Toluene:CH_2Cl_2 = 70:15:15) gave epoxysilane **440c** (213 mg, 25%) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (ddt, J_1 = 17.1 Hz, J_2 = 10.0 Hz, J_3 = 6.7 Hz, 1H, H-6), 5.05 (app. dq, J_1 = 17.1 Hz, J_2 = 1.7 Hz, 1H, H-7$_{trans}$), 4.99 (ddt, J_1 = 10.0 Hz, J_2 = 1.7 Hz, J_3 = 1.2 Hz, 1H, H-7$_{cis}$), 2.79 (ddd, J_1 = 6.0 Hz, J_2 = 5.3 Hz, J_2 = 3.5 Hz, 1H, H-3), 2.30-2.15 (m, 2H, H-5), 1.99 (d, J = 3.5 Hz, 1H, H-2), 1.73 (m, 1H, H-4a), 1.63 (m, 1H, H-4b), 0.05 (s, 9H, H-1) ppm

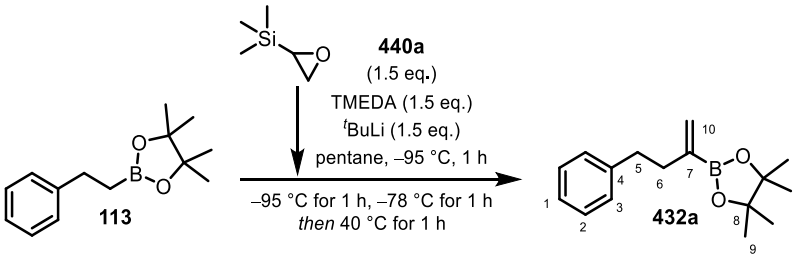
^{13}C NMR (101 MHz, $CDCl_3$): 138.0 (CH), 115.2 (CH_2), 55.8 (CH), 52.0 (CH), 33.5 (CH_2), 30.7 (CH_3), –3.5 (3 × CH_3) ppm

IR (neat): 2957, 1248, 860, 835 cm^{-1}

HRMS (APCI) calculated for $C_9H_{19}OSi$: 171.1200, found 171.1194

R_f = 0.27 (Pentane:Toluene:CH_2Cl_2 = 70:15:15)

4,4,5,5-Tetramethyl-2-(4-phenylbut-1-en-2-yl)-1,3,2-dioxaborolane (**432a**)



According to **GP7** using TMEDA (113 μL, 0.75 mmol), epoxysilane **440a** (103 μL, 0.75 mmol). pentane (5.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (441 μL, 0.75 mmol) and phenethyl boronic ester **113** (117 mg, 0.50 mmol) in pentane (1.00 mL), lithiation time = 1 h. The reaction mixture was stirred at 40 °C for 1 h. Purification of the crude residue by flash column chromatography (Hexane:CH_2Cl_2 = 100:0 → 75:25) gave vinyl boronic ester **432a** (102 mg, 77%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.24 (m, 2H, H-2), 7.21-7.13 (m, 3H, H-1 and H-3), 5.80 (br. d, *J* = 3.5 Hz, 1H, H-10a), 5.60 (br. s, 1H, H-10b), 2.78-2.71 (m, 2H, H-5), 2.50-2.42 (m, 2H, H-6), 1.27 (s, 12H, H-9) ppm

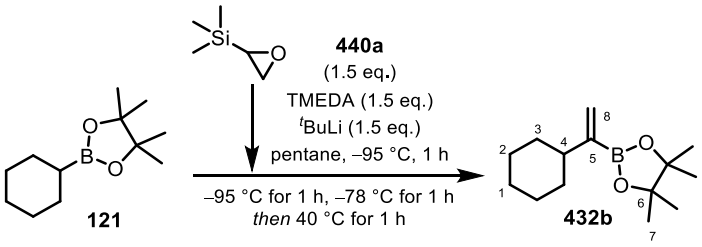
^{13}C NMR (101 MHz, $CDCl_3$): 142.5 (C), 129.6 (CH_2), 128.7 (2 × CH), 128.3 (2 × CH), 125.7 (CH), 83.5 (2 × C), 37.4 (CH_2), 35.9 (CH_2), 24.9 (4 × CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

^{11}B NMR (96 MHz): 30.2 ppm

R_f = 0.43 (Hexane:CH_2Cl_2 = 50:50)

Data in accordance with that reported in the literature.[156]

2-(1-Cyclohexylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**432b**)



According to **GP7** using TMEDA (68 µL, 0.45 mmol), epoxysilane **440a** (62 µL, 0.45 mmol). pentane (3.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (264 µL, 0.45 mmol) and cyclohexyl boronic ester **121** (63.7 mg, 0.30 mmol) in pentane (600 µL), lithiation time = 1 h. The reaction mixture was stirred at 40 °C for 1 h. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 88:12) gave vinyl boronic ester **432b** (48.4 mg, 68%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (br. d, *J* = 3.1 Hz, 1H, H-8a), 5.55 (br. d, *J* = 3.1 Hz, 1H, H-8b), 2.09 (tt, J_1 = 11.7 Hz, J_2 = 2.8 Hz, 1H, H-4), 1.78-1.62 (m, 5H, H-Cy), 1.37-1.28 (m, 2H, H-Cy), 1.26 (s, 12H, H-7), 1.21-1.09 (m, 3H, H-Cy) ppm

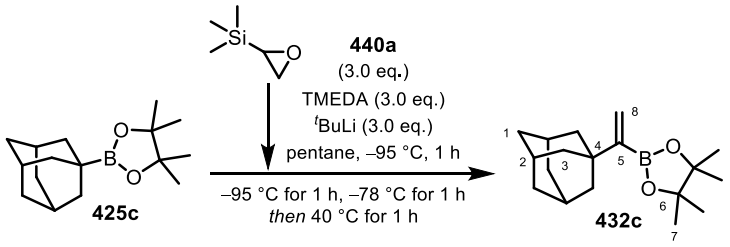
^{13}C NMR (101 MHz, $CDCl_3$): 126.0 (CH_2), 83.3 (2 × C), 43.0 (CH), 32.6 (2 × CH_2), 26.9 (2 × CH_2), 26.5 (CH_2), 24.9 (4 × CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

^{11}B NMR (96 MHz): 29.3 ppm

R_f = 0.16 (Pentane:CH_2Cl_2 = 85:15)

Data in accordance with that reported in the literature.[156]

2-(1-(Adamantan-1-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**432c**)



According to **GP7** using TMEDA (136 µL, 0.90 mmol), epoxysilane **440a** (124 µL, 0.90 mmol). pentane (6.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (528 µL, 0.90 mmol) and adamantyl boronic ester **425c** (79.3 mg, 0.30 mmol) in pentane (600 µL), lithiation time = 1 h. The reaction mixture was stirred at 40 °C for 1 h. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 90:10) gave vinyl boronic ester **432c** (54.0 mg, 62%) as a crystalline white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.64 (d, *J* = 2.8 Hz, 1H, H-8a), 5.48 (br. d, *J* = 2.8 Hz, 1H, H-8b), 1.98 (br. s, 3H, H-2), 1.74-1.64 (m, 12H, H-1 and H-3), 1.27 (s, 12H, H-7), ppm

^{13}C NMR (101 MHz, $CDCl_3$): 123.9 (CH_2), 83.1 (2 × C), 41.6 (3 × CH_2), 37.4 (C), 37.2 (3 × CH_2), 28.9 (3 × CH), 24.9 (4 × CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

^{11}B NMR (96 MHz): 29.7 ppm

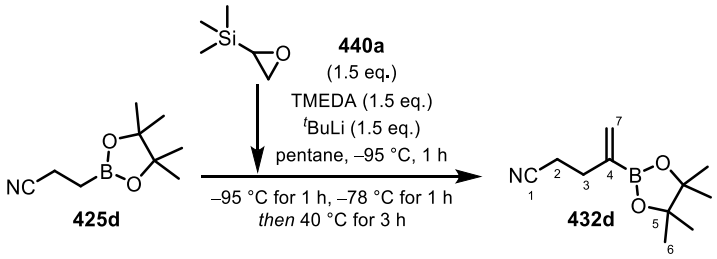
IR (neat): 2912, 2899, 1305, 1143, 1078, 867, 690 cm^{-1}

HRMS (APCI) calculated for $C_{18}H_{30}BO_2$: 289.2333, found 289.2336

M.P. 87-88°C (MeCN)

R_f = 0.19 (Pentane:CH_2Cl_2 = 85:15)

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-enenitrile (**432d**)



According to **GP1** using TMEDA (68 µL, 0.45 mmol), epoxysilane **440a** (62 µL, 0.45 mmol). pentane (3.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (264 µL, 0.45 mmol) and cyano boronic ester **425d** (54.3 mg, 0.30 mmol) in pentane (600 µL), lithiation time = 1 h. The reaction mixture was stirred at 40 °C for 3 h. Purification of the crude residue by flash column chromatography (Pentane:Et_2O = 100:0 → 90:10) gave vinyl boronic ester **432d** (30.2 mg, 49%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94 (br. d, *J* = 2.4 Hz, 1H, H-7a), 5.76 (br. s, 1H, H-7b), 2.54-2.44 (m, 4H, H-2 and H-3), 1.27 (s, 12H, H-6) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 132.5 (CH_2), 119.8 (CN), 83.9 (2 × C), 31.5 (CH_2), 24.9 (4 × CH_3), 17.4 (CH_2) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

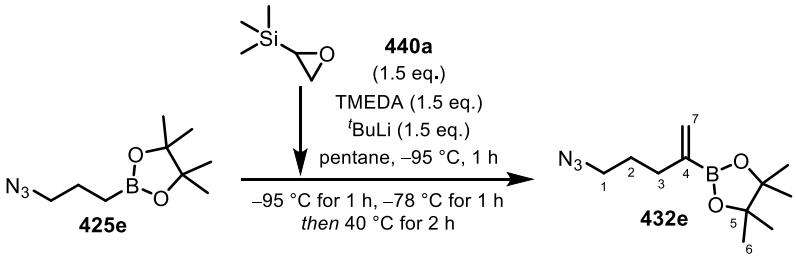
^{11}B NMR (96 MHz): 28.5 ppm

IR (neat): 2978, 2247, 1620, 1371, 1312, 1137, 862, 670 cm^{-1}

HRMS (ESI) calculated for $C_{11}H_{18}BNO_2Na$: 230.1325, found 230.1326

R_f = 0.15 (Pentane:Et_2O = 90:10)

2-(5-Azidopent-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (432e)



According to **GP1** using TMEDA (68 µL, 0.45 mmol), epoxysilane **440a** (62 µL, 0.45 mmol). pentane (3.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (264 µL, 0.45 mmol) and azidyl boronic ester **425e** (63.3 mg, 0.30 mmol) in pentane (600 µL), lithiation time = 1 h. The reaction mixture was stirred at 40 °C for 2 h. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 50:50 – quick purification required due to instability of product on silica gel) gave vinyl boronic ester **432e** (27.1 mg, 38%) as a colourless oil.

^{1}H NMR (400 MHz, C_6D_6): δ 6.16 (d, *J* = 3.3 Hz, 1H, H-7a), 5.62 (br. s, 1H, H-7b), 2.81 (t, *J* = 7.0 Hz, 2H, H-1), 2.23 (t, *J* = 7.4 Hz, 2H, H-3), 1.64 (tt, J_1 = 7.4 Hz, J_2 = 7.0 Hz, 2H, H-2), 1.07 (s, 12H, H-6) ppm

^{13}C NMR (128 MHz, C_6D_6): 130.7 (CH_2), 83.5 (2 × C), 51.0 (CH_2), 33.0 (CH_2), 28.9 (CH_2), 24.9 (4 × CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

^{11}B NMR (96 MHz): 28.9 ppm

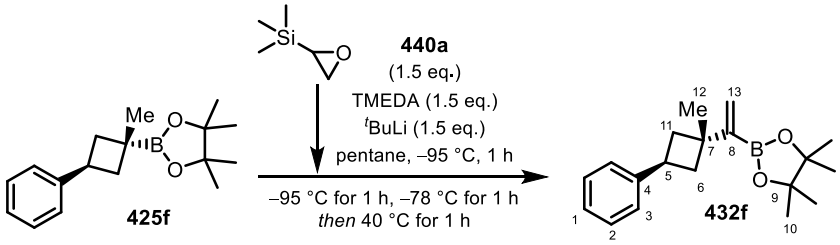
IR (neat): 2979, 2932, 2093, 1359, 1309, 1139, 948, 859, 670 cm^{-1}

HRMS (ESI) calculated for $C_{11}H_{20}BN_3O_2Na$: 260.1543, found 260.1532

R_f = 0.20 (Pentane:CH_2Cl_2 = 50:50)

Note: Compound is unstable and must be used immediately after isolation or stored in a freezer under an inert atmosphere where it is stable for up to a month

4,4,5,5-Tetramethyl-2-(1-methyl-3-phenylcyclobutyl)vinyl)-1,3,2-dioxaborolane (432f)



According to **GP7** using TMEDA (68 µL, 0.45 mmol), epoxysilane **440a** (62 µL, 0.45 mmol). pentane (3.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (264 µL, 0.45 mmol) and cyclobutyl boronic ester **425f** (81.6 mg, 0.30 mmol) in pentane (600 µL), lithiation time = 1 h. The reaction mixture was stirred at 40 °C for 1 h. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 80:20) gave vinyl boronic ester **432f** (64.4 mg, 72%, >95:5 d.r.) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (dd, J_1 = 7.5 Hz, J_2 = 7.2 Hz, 2H, H-2), 7.22 (d, J = 7.5 Hz, 2H, H-3), 7.16 (t, J = 7.2 Hz, 1H, H-1), 5.90 (d, J = 2.5 Hz, 1H, H-13a), 5.77 (br. d, J = 2.5 Hz, 1H, H-13b), 3.27 (p, J = 9.2 Hz, 1H, H-5), 2.67-2.60 (m, 2H, H-6a and H-11a), 2.07-1.99 (m, 2H, H-6b and H-11b), 1.29 (s, 12H, H-10), 1.24 (s, 3H, H-12) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 146.6 (C), 128.3 (2 × CH), 126.6 (2 × CH), 125.6 (CH), 125.1 (CH_2), 83.4 (2 × C), 40.7 (2 × CH_2), 40.0 (C), 33.5 (CH), 30.4 (CH_3), 24.9 (4 × CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

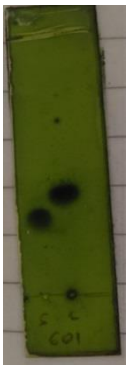
^{11}B NMR (96 MHz): 29.4 ppm

IR (neat): 2977, 1371, 1351, 1303, 1146, 939, 752, 700 cm^{-1}

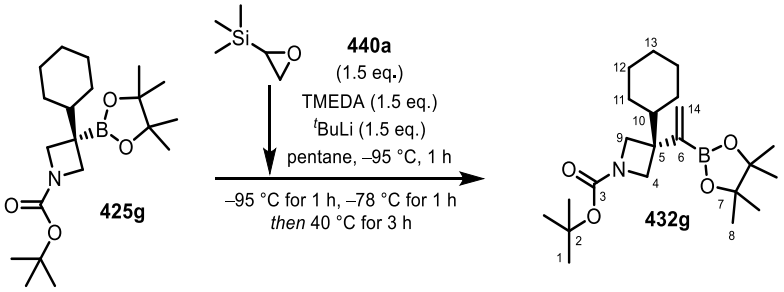
HRMS (APCI) calculated for $C_{19}H_{28}BO_2$: 299.2177, found 299.2178

M.P. 48-49 °C (MeCN)

R_f = 0.50 (Pentane:CH_2Cl_2 = 70:30)



tert-Butyl 3-cyclohexyl-3-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)azetidine-1-carboxylate (**432g**)



According to **GP7** using TMEDA (68 µL, 0.45 mmol), epoxysilane **440a** (62 µL, 0.45 mmol). pentane (3.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (264 µL, 0.45 mmol) and azetidinyl boronic ester **425g** (109.5 mg, 0.30 mmol) in pentane/Et_2O/THF (1:1:1, 900 µL), lithation time = 1 h. The reaction mixture was stirred at 40 °C for 3 h. Purification of the crude residue by flash column chromatography (Pentane:Et_2O = 100:0 → 90:10) gave vinyl boronic ester **432g** (65.0 mg, 55%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.02 (br. d, *J* = 2.6 Hz, 1H, H-14a), 5.44 (br. d, *J* = 2.6 Hz, 1H, H-14b), 3.93 (br.d, *J* = 8.7 Hz, 2H, H-4a and H-9a), 3.81 (d, *J* = 8.7 Hz, 2H, H-4b and H-9b), 1.79-1.56 (m, 5H, H-Cy), 1.44 (s, 9H, H-1), 1.27-1.03 (m, 16H, H-8 and H-Cy), 0.89-0.75 (m, 2H, H-Cy) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 156.7 (CO), 130.2 (CH_2), 83.6 (2 × C), 79.1 (C), 58.1 (CH_2), 57.1 (CH_2), 45.9 (C), 45.7 (CH), 28.6 (3 × CH_3), 27.7 (2 × CH_2), 26.8 (2 × CH_2), 26.6 (CH_2), 24.8 (4 × CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

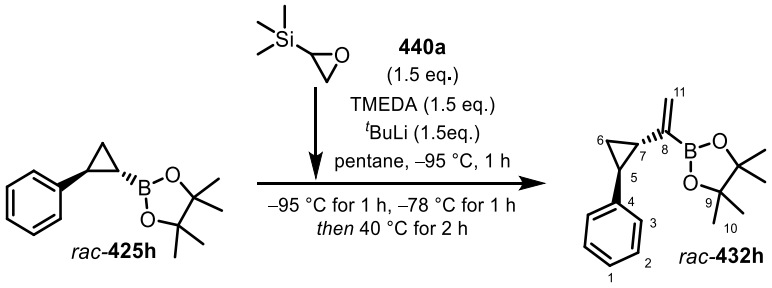
^{11}B NMR (96 MHz): 28.9 ppm

IR (neat): 2927, 1700, 1401, 1134, 956, 731 cm^{-1}

HRMS (ESI) calculated for $C_{22}H_{38}BNO_4Na$: 414.2790, found 414.2796

R_f = 0.33 (Pentane:Et_2O = 80:20)

rac-4,4,5,5-Tetramethyl-2-(1-((1*S*,2*S*)-2-phenylcyclopropyl)vinyl)-1,3,2-dioxaborolane _rac_-(432h)



According to **GP7** using TMEDA (68 µL, 0.45 mmol), epoxysilane **440a** (62 µL, 0.45 mmol). pentane (3.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (264 µL, 0.45 mmol) and cyclopropyl boronic ester **425h** (73.3 mg, 0.30 mmol) in pentane (600 µL), lithation time = 1 h. The reaction mixture was stirred at 40 °C for 5 h. Purification of the crude residue by flash column chromatography on basic silica gel (*see* Materials & Reagents)(Pentane:CH_2Cl_2 = 100:0 → 70:30 – quick purification required due to instability of product on silica gel) gave vinyl boronic ester *rac*-**432h** (41.0 mg, 51%) as a milky white oil.

^{1}H NMR (400 MHz, C_6D_6): δ 7.11 (t, J = 7.6 Hz, 2H, H-2), 7.06-6.99 (m, 3H, H-1 and H-3), 6.13 (d, J = 3.2 Hz, 1H, H-11a), 5.64 (br. d, J = 3.2 Hz, 1H, H-11b), 2.33 (ddd, J_1 = 8.6 Hz, J_2 = 5.6 Hz, J_3 = 4.8 Hz, 1H, H-5), 2.05 (ddd, J_1 = 8.7 Hz, J_2 = 5.8 Hz, J_3 = 4.8 Hz, 1H, H-7), 1.46 (ddd, J_1 = 8.6 Hz, J_2 = 5.8 Hz, J_3 = 4.5 Hz, 1H, H-6a), 1.17 (ddd, J_1 = 8.7 Hz, J_2 = 5.6 Hz, J_3 = 4.5 Hz, 1H, H-6b), 1.02 (s, 6H, H-10a), 1.01 (s, 6H, H-10b) ppm

^{13}C NMR (128 MHz, C_6D_6): 143.5 (C), 128.6 (2 × CH), 126.9 (CH_2), 126.4 (2 × CH), 125.7 (CH), 83.4 (2 × C), 28.9 (CH), 26.5 (CH), 24.9 (2 × CH_3), 24.8 (2 × CH_3), 17.9 (CH_2) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

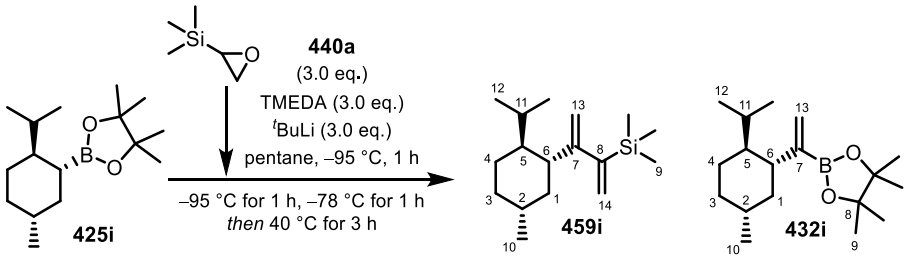
^{11}B NMR (96 MHz): 28.7 ppm

IR (neat): 3073, 2972, 1308, 1133, 967, 849, 695 cm^{-1}

HRMS (ESI) calculated for $C_{17}H_{24}BO_2$: 271.1867, found 271.1876

R_f = 0.36 (Pentane:CH_2Cl_2 = 60:40)

(3-((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)buta-1,3-dien-2-yl)trimethylsilane (459i) and 2-(1-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (432i)



According to **GP7** using TMEDA (136 µL, 0.90 mmol), epoxysilane **440a** (124 µL, 0.90 mmol). pentane (6.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (528 µL, 0.90 mmol) and menthyl boronic ester **425i** (79.8 mg, 0.30 mmol) in pentane (600 µL), lithiation time = 1 h. The reaction mixture was stirred at 40 °C for 3 h. Purification of the crude residue by flash column chromatography (Pentane:toluene = 100:0 → 90:10) gave vinyl silane **459i** (16.2 mg, 20%) as a colourless oil and vinyl boronic ester **432i** (26.8 mg, 31%, >95:5 d.r.) as a colourless oil.

Vinyl silane **459i**

[α]$^{22}_{D}$: – 33 ° (*c* 0.37, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72 (br. d, *J* = 2.7 Hz, 1H, H-14a), 5.40 (br. d, *J* = 2.7 Hz, 1H, H-14b), 4.90 (s, 1H, H-13a), 4.82 (s, 1H, H-13b), 2.10 (td, J_1 = 11.5 Hz, J_2 = 3.2 Hz, 1H, H-6), 1.74-1.58 (d. sept, J_1 = 7.1 Hz, J_2 = 2.2 Hz, 1H, H-11), 1.81-1.65 (m, 3H, H-1a, H-3a and H-4a), 1.39-1.22 (m, 2H, H-2 and H-5), 1.10-0.81 (m, 9H, H-1b, H-3b, H-4b, H-10 and H-12a), 0.66 (d, *J* = 6.9 Hz, 3H, H-12b), 0.15 (s, 9H, H-9) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 155.7 (C), 154.6 (C), 124.6 (CH_2), 110.4 (CH_2), 46.9 (CH), 45.6 (CH), 44.7 (CH_2), 35.4 (CH_2), 33.4 (CH), 27.0 (CH), 24.7 (CH_2), 22.7 (CH_3), 21.9 (CH_3), 16.2 (CH_3), –0.1 (3 × CH_3) ppm

IR (neat): 2953, 2919, 1455, 1248, 887, 845 cm^{-1}

HRMS (APCI) calculated for $C_{17}H_{33}Si$: 265.2346, found 265.2341

R_f = 0.96 (Pentane:toluene = 80:20)

Vinyl boronic ester **432i**

[α]$^{22}_{D}$: – 30 ° (*c* 0.74, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.73 (d, *J* = 3.6 Hz, 1H, H-13a), 5.57 (br. d, *J* = 3.6 Hz, 1H, H-13b), 2.06 (td, J_1 = 11.6 Hz, J_2 = 3.4 Hz, 1H, H-6), 1.74-1.58 (m, 3H, H-3a, H-4a and H-11), 1.53-1.32 (m, 3H, H-1_{eq}, H-2 and H-5), 1.25 (s, 6H, H-9a), 1.24 (s, 6H, H-9b), 1.13 (app. dd, J_1 = 12.1 Hz, J_2 = 11.6 Hz, 1H, H-1_{ax}), 1.03-0.89 (m, 2H, H-3b and H-4b), 0.86 (d, *J* = 6.5 Hz, 3H, H-10), 0.84 (d, *J* = 7.5 Hz, 3H, H-12a), 0.66 (d, *J* = 7.5 Hz, 3H, H-12b) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 128.6 (CH_2), 83.1 (2 × C), 48.8 (CH), 45.7 (CH), 43.3 (CH_2), 35.5 (CH_2), 33.2 (CH), 28.2 (CH), 25.0 (2 × CH_3), 24.7 (2 × CH_3), 24.5 (CH_2), 22.8 (CH_3), 21.6 (CH_3), 15.2 (CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

^{11}B NMR (96 MHz): 29.4 ppm

IR (neat): 2953, 2916, 1370, 1303, 1143, 948, 848, 697 cm^{-1}

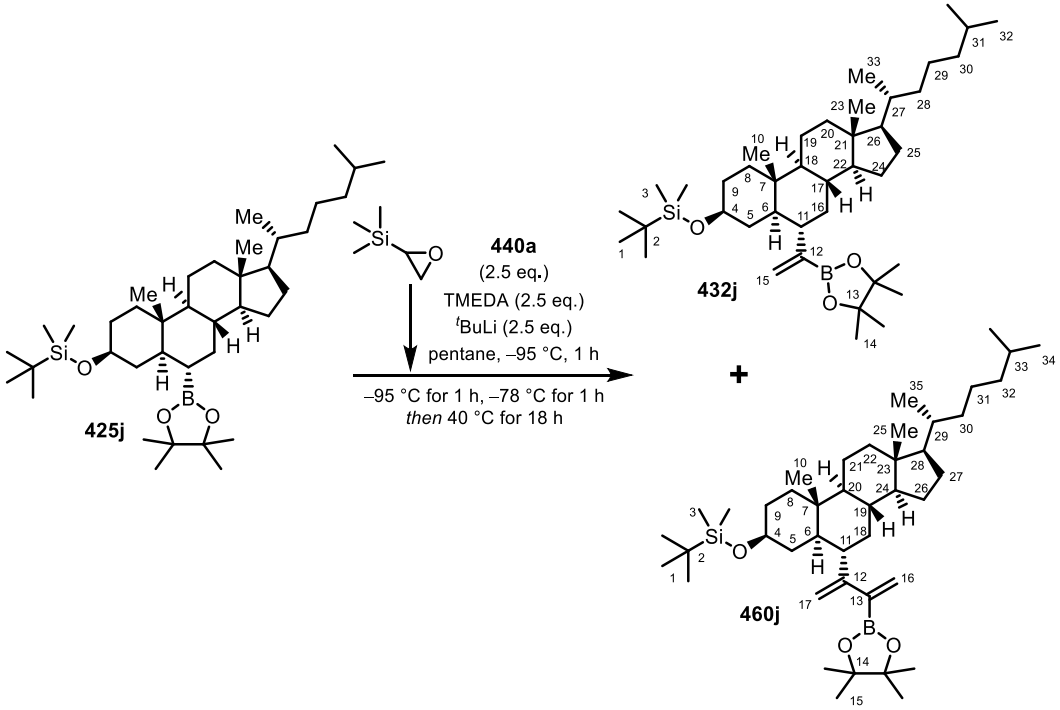
HRMS (APCI) calculated for $C_{18}H_{34}BO_2$: 293.2646, found 293.2648

R_f = 0.45 (Pentane:toluene = 75:25)

***tert*-Butyl(((3*S*,5*R*,6*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-6-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)hexadecahydro-1H-cyclopenta[*a*]phenanthren-3-yl)oxy)dimethylsilane (432j)**

and

***tert*-butyl(((3*S*,5*R*,6*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-6-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)buta-1,3-dien-2-yl)hexadecahydro-1H-cyclopenta[*a*]phenanthren-3-yl)oxy)dimethylsilane (460j)**



According to **GP7** using TMEDA (57 µL, 0.38 mmol), epoxysilane **440a** (52 µL, 0.38 mmol). pentane (3.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (223 µL, 0.38 mmol) and cholesteryl boronic ester **425j** (94.3 mg, 0.15 mmol) in Et_2O (600 µL), lithiation time = 1 h. The reaction mixture was stirred at 40 °C for 18 h. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 80:20) gave vinyl boronic ester **432j** (44.9 mg, 46%) as a colourless oil and over-homologation product **460j** (7.3 mg, 7%) as a white solid.

Vinyl boronic ester **432j**

$[\alpha]^{22}_D$: + 17 ° (*c* 1.23, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72 (d, *J* = 3.6 Hz, 1H, H-15a), 5.52 (br. d, *J* = 3.6 Hz, 1H, H-15b), 3.45 (m, 1H, H-4), 2.06 (td, J_1 = 11.8 Hz, J_2 = 3.0 Hz, 1H, H-11), 1.99-1.59 (m, 4H, H-cholesteryl), 1.52-0.61 (m, 61H, H-1, H-14 and H-cholesteryl), 0.02 (s, 3H, H-3a), 0.01 (s, 3H, H-3b) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 128.7 (CH_2), 83.1 (2 × C), 72.8, (CH), 56.5 (CH), 56.4 (CH), 54.3 (CH), 45.1 (CH), 42.8 (C), 40.3 (CH_2), 39.7 (CH_2), 39.2 (CH_2), 37.6 (CH_2), 36.3 (CH_2), 35.9 (CH_2), 35.8 (CH and CH_2), 35.3 (CH), 32.0 (CH_2), 30.5 (CH), 28.5 (CH_2), 28.2 (CH), 26.1 (3 × CH_3), 25.0 (2 × CH_3), 24.8 (2 × CH_3), 24.3 (CH_2), 23.9 (CH_2), 23.0 (CH_3), 22.7 (CH_3), 21.4 (C), 18.9 (CH_3), 18.4 (C), 13.3 (CH_3), 12.2 (CH_3), –4.4 (2 × CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

^{11}B NMR (96 MHz): 29.0 ppm

IR (neat): 2930, 2854, 1469, 1359, 1141, 1096, 834, 772 cm^{-1}

HRMS (MALDI) calculated for $C_{41}H_{75}BO_3SiNa$: 677.5478, found 677.5485

R_f = 0.49 (Pentane:CH_2Cl_2 = 50:50)

Bis vinyl boronic ester **460j**

[α]$^{22}_{D}$: + 7 ° (*c* 0.25, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (br. s, 2H, H-16), 5.19 (br. s, 1H, H-17a), 4.83 (br. s, 1H, H-17b), 3.43 (m, 1H, H-4), 2.19 (m, 1H, H-11), 1.99-1.60 (m, 6H, H-cholesteryl), 1.52-0.61 (m, 59H, H-1, H-15 and H-cholesteryl), 0.01 (s, 6H, H-3) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 154.5 (C), 127.6 (CH_2), 111.7 (CH_2), 83.6 (2 × C), 72.8, (CH), 56.5 (CH), 56.4 (CH), 54.5 (CH), 49.6 (CH), 42.7 (C), 40.7 (CH_2), 40.3 (CH_2), 39.7 (CH_2), 37.7 (CH_2), 36.3 (CH_2), 36.2 (CH_2), 36.0 (CH), 35.6 (CH), 34.6 (CH_2), 32.0 (CH_2), 30.5 (CH), 28.4 (CH_2), 28.2 (CH), 26.2 (3 × CH_3), 25.0 (2 × CH_3), 24.9 (2 × CH_3), 24.4 (CH_2), 24.0 (CH_2), 23.0 (CH_3), 22.7 (CH_3), 21.5 (C), 18.9 (CH_3), 18.5 (C), 13.3 (CH_3), 12.2 (CH_3), –4.3 (CH_3), –4.5 (CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

^{11}B NMR (96 MHz): 28.6 ppm

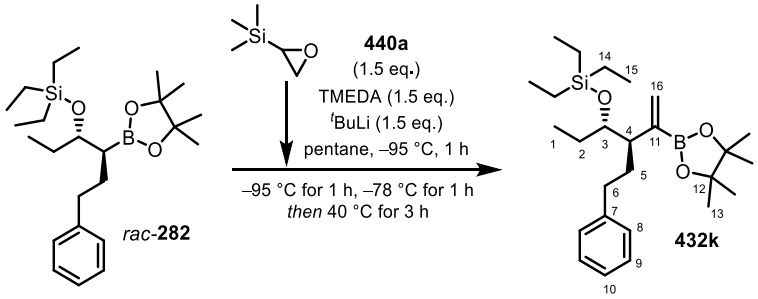
IR (neat): 2948, 2930, 2853, 1460, 1372, 1145, 1098, 948, 835, 773 cm^{-1}

HRMS (MALDI) calculated for $C_{43}H_{77}BO_3SiNa$: 703.5635, found 703.5644

M.P. 123-124°C (MeCN)

R_f = 0.40 (Pentane:CH_2Cl_2 = 50:50)

***rac*-triethyl(((3*S*, 4*R*)-4-phenethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-3-yl)oxy)silane *rac*-(432k)**



According to **GP7** using TMEDA (45 μL, 0.30 mmol), epoxysilane **440a** (41 μL, 0.30 mmol). pentane (2.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (176 μL, 0.30 mmol) and β-oxyboronic ester *rac*-**282** (83.6 mg, 0.20 mmol) in pentane (400 μL), lithiation time = 1 h. The reaction mixture was stirred for 1 h at rt, before heating at 40 °C for 3 h. Purification of the crude residue by flash column chromatography (100% $CHCl_3$) gave vinyl boronic ester *rac*-**432k** (42.0 mg, 47%, d.r. >95:5) as a colourless oil and recovered starting boronic ester *rac*-**282** (22.0 mg, 26%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (t, *J* = 7.5 Hz, 2H, H-9), 7.19-7.12 (m, 3H, H-8 and H-10), 6.00 (br. d, *J* = 3.2 Hz, 1H, H-16a), 5.72 (br. d, *J* = 3.2 Hz, 1H, H-16b), 3.65 (dt, J_1 = 7.9 Hz, J_2 = 4.0 Hz, 1H, H-3), 2.62 (ddd, J_1 = 14.1 Hz, J_2 = 7.5 Hz, J_3 = 7.0 Hz, 1H, H-6a), 2.46 (m, 1H, H-4), 2.39 (m, 1H, H-6b), 1.92-1.84 (m, 2H, H-5), 1.40 (m, 1H, H-2a), 1.29 (m, 1H, 2b), 1.27 (s, 12H, H-13), 0.97 (t, *J* = 7.8 Hz, 9H, H-15), 0.82 (t, *J* = 7.3 Hz, 3H, H-1), 0.59 (q, *J* = 8.0 Hz, 6H, H-14) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 143.5 (C), 131.3 (CH_2), 128.6 (2 × CH), 128.3 (2 × CH), 125.6 (CH), 83.4 (2 × C), 76.2 (CH), 50.1 (CH), 34.6 (CH_2), 29.2 (CH_2), 25.3 (CH_2), 25.1 (2 × CH_3), 24.8 (2 × CH_3), 10.6 (CH_3), 7.2 (3 × CH_3), 5.3 (3 × CH_2) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

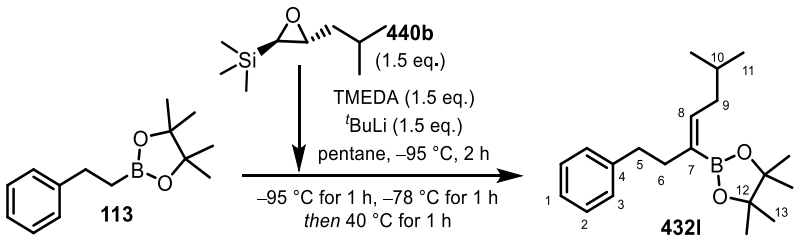
^{11}B NMR (96 MHz): 29.4 ppm

IR (neat): 2954, 2876, 1371, 1306, 1141, 1006, 849, 742, 698 cm^{-1}

HRMS (MALDI) calculated for $C_{26}H_{45}BO_3SiNa$: 467.3128, found 467.3120

R_f = 0.39 ($CHCl_3$)

(*E*)-4,4,5,5-Tetramethyl-2-(6-methyl-1-phenylhept-3-en-3-yl)-1,3,2-dioxaborolane (432l)



According to **GP7** using TMEDA (45 µL, 0.30 mmol), epoxysilane **440b** (51.7 mg, 0.30 mmol). pentane (2.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (176 µL, 0.30 mmol) and phenethyl boronic ester **113** (46.6 mg, 0.20 mmol) in pentane (200 µL), lithiation time = 2 h. The reaction mixture was stirred at 40 °C for 1 h. Purification of the crude residue by flash column chromatography (Petroleum ether 40-60:CH_2Cl_2 = 80:20) gave vinyl boronic ester **432l** (18.8 mg, 30%, >98:2 *E/Z*) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.23 (m, 2H, H-2), 7.20-7.12 (m, 3H, H-1 and H-3), 6.00 (br. t, *J* = 7.4 Hz, 1H, H-8), 2.71-2.65 (m, 2H, H-5), 2.40 (br. t, *J* = 7.4 Hz, 2H, H-6), 2.19 (app. t, *J* = 7.4 Hz, 2H, H-9), 1.57 (m, 1H, H-10), 1.28 (s, 12H, H-13), 0.85 (d, *J* = 6.7 Hz, 6H, H-11) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 146.0 (CH), 142.9 (C), 128.8 (2 × CH), 128.3 (2 × CH), 125.6 (CH), 83.0 (2 × C), 40.2 (CH_2), 39.2 (CH_2), 37.2 (CH_2), 29.2 (CH), 25.0 (4 × CH_3), 22.5 (2 × CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

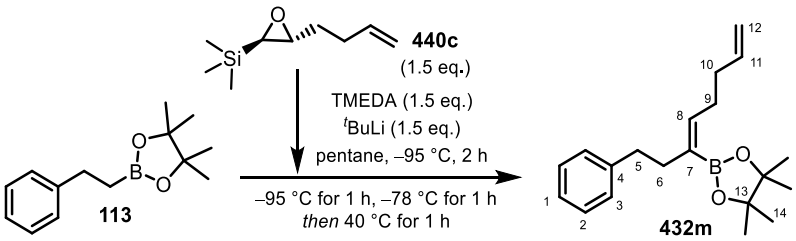
^{11}B NMR (96 MHz): 29.5 ppm

IR (neat): 2977, 2922, 1404, 1266, 1143, 1078, 860, 697 cm^{-1}

HRMS (APCI) calculated for $C_{20}H_{32}BO_2$: 315.2490, found 315.2475

R_f = 0.60 (Pentane:CH_2Cl_2 = 70:30)

(*E*)-4,4,5,5-Tetramethyl-2-(6-methyl-1-phenylhept-3-en-3-yl)-1,3,2-dioxaborolane (432m)



According to **GP7** using TMEDA (45 µL, 0.30 mmol), epoxysilane **440c** (51.0 mg, 0.30 mmol). pentane (2.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (176 µL, 0.30 mmol) and phenethyl boronic ester **113** (46.6 mg, 0.20 mmol) in pentane (200 µL), lithiation time = 2 h. The reaction mixture was stirred at 40 °C for 1 h. Purification of the crude residue by flash column chromatography (Petroleum ether 40-60:CH_2Cl_2 = 80:20) gave vinyl boronic ester **432m** (45.8 mg, 73%, >98:2 *E/Z*) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.23 (m, 2H, H-2), 7.10-7.13 (m, 3H, H-1 and H-3), 5.99 (br. t, J = 7.6 Hz, 1H, H-8), 5.80 (ddt, J_1 = 16.9 Hz, J_2 = 9.9 Hz, J_3 = 6.6 Hz, 1H, H-11), 4.99 (app. dq, J_1 = 16.9 Hz, J_2 = 1.6 Hz, 1H, H-12$_{trans}$), 4.99 (ddt, J_1 = 9.9 Hz, J_2 = 1.7 Hz, J_3 = 1.2 Hz, 1H, H-12$_{cis}$), 2.70-2.64 (m, 2H, H-5), 2.44-2.35 (m, 4H, H-6 and H-9), 2.12-2.04 (m, 2H, H-10), 1.28 (s, 12H, H-14) ppm

^{13}C NMR (126 MHz, $CDCl_3$): 146.2 (CH), 142.8 (C), 138.7 (CH), 128.8 (2 × CH), 128.3 (2 × CH), 125.6 (CH), 114.5 (CH_2), 83.0 (2 × C), 39.0 (CH_2), 37.1 (CH_2), 34.3 (CH_2), 30.6 (CH_2), 25.0 (4 × CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

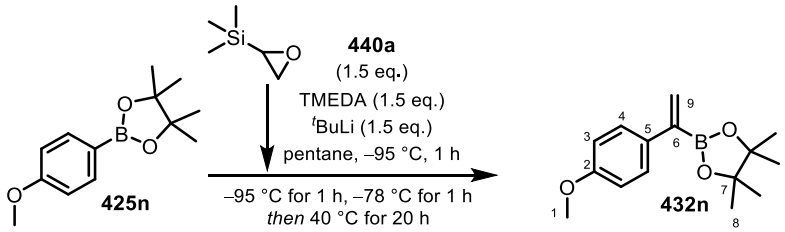
^{11}B NMR (96 MHz): 29.7 ppm

IR (neat): 2996, 2956, 1405, 1260, 1143, 1046, 733, 698 cm^{-1}

HRMS (ESI) calculated for $C_{20}H_{30}BO_2$: 313.2333, found 313.2347

R_f = 0.61 (Pentane:CH_2Cl_2 = 70:30)

2-(1-(4-Methoxyphenyl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**432n**)



According to **GP7** using TMEDA (68 µL, 0.45 mmol), epoxysilane **440a** (62 µL, 0.45 mmol). pentane (3.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (264 µL, 0.45 mmol) and *p*-methoxyphenyl boronic ester **425n** (63.7 mg, 0.30 mmol) in pentane (600 µL), lithiation time = 1 h. The reaction mixture was stirred at 40 °C for 20 h. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 60:40) gave vinyl boronic ester **432n** (61.8 mg, 79%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.9 Hz, 2H, H-4), 6.86 (d, *J* = 8.9 Hz, 2H, H-3), 6.01 (br. d, *J* = 2.8 Hz, 1H, H-9a), 5.96 (d, *J* = 2.8 Hz, 1H, H-9b), 3.80 (s, 3H, H-1), 1.32 (s, 12H, H-7) ppm

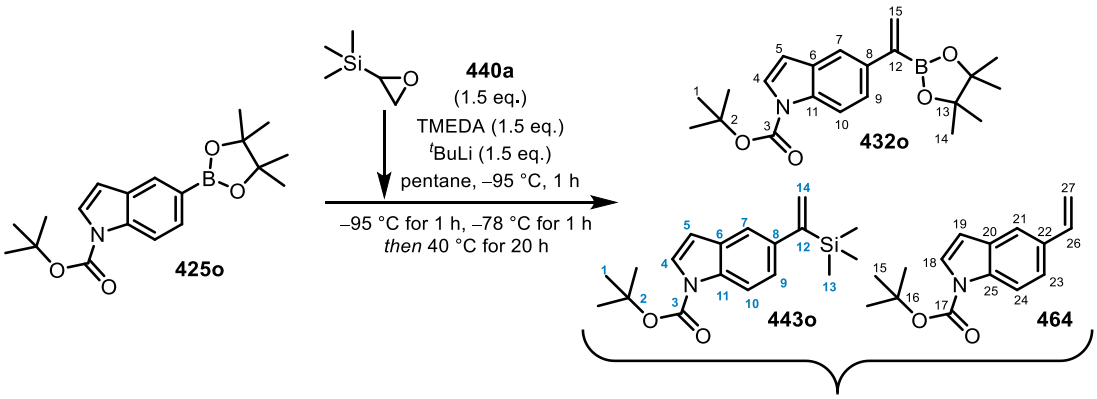
^{13}C NMR (101 MHz, $CDCl_3$): 159.0 (C), 134.1 (C), 129.1 (CH_2), 128.4 (2 × CH), 113.8 (2 × CH), 83.9 (2 × C), 55.4 (CH_3), 25.0 (4 × CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

^{11}B NMR (96 MHz): 29.6 ppm

R_f = 0.29 (Pentane:CH_2Cl_2 = 50:50)

Data in accordance with that reported in the literature.[213]

tert-Butyl 5-(1-(trimethylsilyl)vinyl)-1H-indole-1-carboxylate (443o), _tert_-butyl 5-vinyl-1H-indole-1-carboxylate (464) and _tert_-butyl 5-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1H-indole-1-carboxylate (432o)



According to **GP7** using TMEDA (68 µL, 0.45 mmol), epoxysilane **440a** (62 µL, 0.45 mmol). pentane (3.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (264 µL, 0.45 mmol) and indolyl boronic ester **425o** (103.0 mg, 0.30 mmol) in Et_2O (600 µL), lithiation time = 1 h. The reaction mixture was stirred at 40 °C for 20 h. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 60:40) gave an inseparable mixture of vinyl silane **443o** and styrene **464** (2.3:1, 24.5 mg, 28%) as a colourless oil and boronic ester **432o** (34.0 mg, 31%) as a colourless oil.

Vinyl silane **443o** and styrene **464**

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.6 Hz, 1H, H-24), 8.04 (d, J = 8.6 Hz, 1H, H-**10**), 7.60-7.55 (m, 3H, H-**4**, H-18 and H-21), 7.41 (dd, J_1 = 8.6 Hz, J_2 = 1.8 Hz, 1H, H-23), 7.35 (d, J = 1.5 Hz, 1H, H-**7**), 7.14 (dd, J_1 = 8.6 Hz, J_2 = 1.5 Hz, 1H, H-**9**), 6.81 (dd, J_1 = 17.6 Hz, J_2 = 11.0 Hz, 1H, H-26), 6.56-6.53 (m, 2H, H-**5**, H-19), 5.85 (d, J = 3.1 Hz, 1H, H-**14a**), 5.74 (dd, J_1 = 17.6 Hz, J_2 = 1.0 Hz, 1H, H-27$_{trans}$), 5.62 (d, J = 3.1 Hz, 1H, H-**14b**), 5.21 (dd, J_1 = 11.0 Hz, J_2 = 1.0 Hz, 1H, H-27$_{cis}$), 1.67 (s, 18H, H-**1**, H-15), 0.19 (s, 9H, H-**13**) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 153.8 (**C**O), 149.9 (CO), 139.7 (**C**), 137.3 (CH), 135.0 (C), 134.0 (**C**), 132.5 (**C** and C), 131.0 (C), 130.8 (**C**), 127.0 (**C**H_2), 126.5 (CH), 126.2 (**CH**), 123.6 (**CH**), 122.6 (CH), 119.0 (CH), 118.9 (**CH**), 115.2 (CH), 114.8 (**CH**), 112.6 (CH_2), 107.6 (CH), 107.5 (**CH**), 83.9 (C), 83.7 (**C**), 28.3 (3 × **C**H_3 and 3 × CH_3), –0.7 (3 × **C**H_3) ppm

IR (neat): 2980, 1731, 1366, 1158, 836, 731 cm^{-1}

HRMS (ESI) calculated for $C_{18}H_{26}NO_2Si$: 316.1727, found 316.1721 (**443o**)

R_f = 0.38 (**443o**) and 0.40 (**464**) (Pentane:CH_2Cl_2 = 75:25)

Data for **464** in accordance with that reported in the literature.[214]

Vinyl boronic ester **432o**

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.1 Hz, 1H, H-10), 7.67 (d, *J* = 1.7 Hz, 1H, H-7), 7.56 (d, *J* = 3.7 Hz, 1H, H-4), 7.44 (dd, J_1 = 8.1 Hz, J_2 = 1.7 Hz, 1H, H-9), 6.56 (br. d, *J* = 3.7 Hz, 1H, H-5), 6.10 (d, *J* = 3.0 Hz, 1H, H-15a), 6.05 (d, *J* = 3.0 Hz, 1H, H-15b), 1.67 (s, 9H, H-1), 1.34 (s, 12H, H-14) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 145.0 (CO), 136.3 (C), 134.6 (C), 130.8 (C), 130.2 (CH_2), 126.1 (CH), 123.9 (CH), 119.7 (CH), 114.9 (CH), 107.8 (C), 83.9 (2 × C), 83.7 (C), 28.4 (3 × CH_3) 25.0 (4 × CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

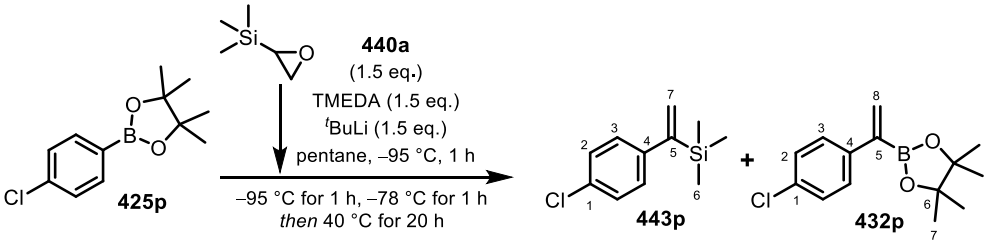
^{11}B NMR (96 MHz): 29.7 ppm

IR (neat): 2977, 1732, 1354, 1140, 1084, 848, 732 cm^{-1}

HRMS (ESI) calculated for $C_{21}H_{28}BNO_4Na$: 392.2007, found 399.2020

R_f = 0.43 (Pentane:CH_2Cl_2 = 50:50)

(1-(4-Chlorophenyl)vinyl)trimethylsilane (443p) and 2-(1-(4-chlorophenyl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (432p)



According to **GP7** using TMEDA (68 µL, 0.45 mmol), epoxysilane **440a** (62 µL, 0.45 mmol). pentane (3.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (264 µL, 0.45 mmol) and *p*-chlorophenyl boronic ester **425p** (71.4 mg, 0.30 mmol) in pentane (600 µL), lithiation time = 1 h. The reaction mixture was stirred at 40 °C for 20 h. Purification of the crude residue by flash column chromatography (Pentane:Me_2CO = 100:0 → 99.5:0.5) gave vinyl silane **443p** (40.0 mg, 63%) as a colourless oil and boronic ester **432p** (22.5 mg, 23% - contains *ca.* 10% starting boronic ester **425p** impurity) as a colourless oil.

Vinyl silane **443p**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.4 Hz, 2H, H-2), 7.09 (d, *J* = 8.4 Hz, 2H, H-3), 5.80 (d, *J* = 3.0 Hz, 1H, H-7a), 5.61 (d, *J* = 3.0 Hz, 1H, H-7b), 0.16 (s, 9H, H-6) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 152.6 (C), 143.4 (C), 132.2 (C), 128.4 (2 × CH), 128.2 (2 × CH), 127.8 (CH_2), –0.8 (3 × CH_3) ppm

R_f = 0.94 (Pentane:CH_2Cl_2 = 50:50)

Data in accordance with that reported in the literature.[215]

Vinyl boronic ester **432p**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.6 Hz, 2H, H-2), 7.28 (d, *J* = 8.6 Hz, 2H, H-3), 6.08-6.05 (m, 2H, H-8), 1.32 (s, 12H, H-7) ppm

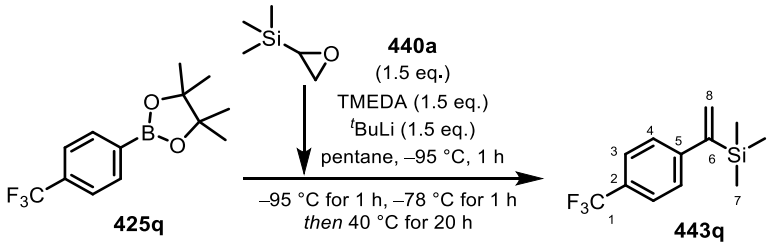
^{13}C NMR (101 MHz, $CDCl_3$): 140.0 (C), 136.3 (C), 131.5 (CH_2), 128.7 (2 × CH), 128.4 (2 × CH), 84.1 (2 × C), 25.0 (4 × CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

^{11}B NMR (96 MHz): 29.7 ppm

R_f = 0.68 (Pentane:CH_2Cl_2 = 50:50)

Data in accordance with that reported in the literature. [216]

Trimethyl(1-(4-(trifluoromethyl)phenyl)vinyl)silane (**443q**)



According to **GP7** using TMEDA (68 µL, 0.45 mml), epoxysilane **440a** (62 µL, 0.45 mmol). pentane (3.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (264 µL, 0.45 mmol) and *p*-trifluoromethylphenyl boronic ester **425q** (81.6 mg, 0.30 mmol) in pentane (600 µL), lithiation time = 1 h. The reaction mixture was stirred at 40 °C for 20 h. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 99:1) gave vinyl silane **443q** (40.3 mg, 55%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.0 Hz, 2H, H-3), 7.25 (d, *J* = 8.0 Hz, 2H, H-4), 5.83 (d, *J* = 2.8 Hz, 1H, H-8a), 5.68 (d, *J* = 2.8 Hz, 1H, H-8b), 0.17 (s, 9H, H-7) ppm

^{13}C NMR (126 MHz, $CDCl_3$): 153.0 (C), 148.8 (C), 128.8 (CH_2), 128.5 (q, ^{2}J = 32.7 Hz, C) 127.1 (2 × CH), 125.2 (q, ^{3}J = 3.8 Hz, 2 × CH), 124.5 (q, ^{1}J = 271 Hz, CF_3), –0.9 (3 × CH_3) ppm

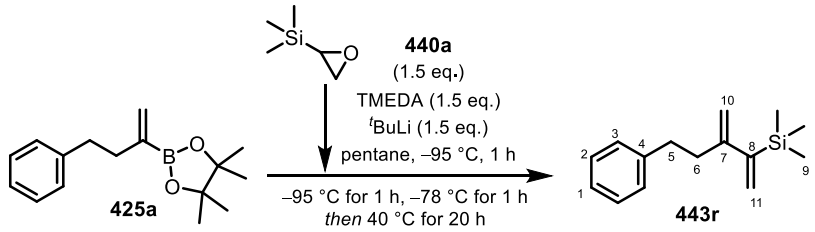
^{19}F NMR (377 MHz, $CDCl_3$): –62.3 ppm

IR (neat): 2968, 1323, 1123, 837, 760 cm^{-1}

HRMS (EI) calculated for $C_{12}H_{15}F_3Si$: 244.0890, found 244.0889

R_f = 0.78 (Pentane:CH_2Cl_2 = 95:5)

Trimethyl(3-methylene-5-phenylpent-1-en-2-yl)silane (**443r**)



According to **GP7** using TMEDA (68 µL, 0.45 mmol), epoxysilane **440a** (62 µL, 0.45 mmol). pentane (3.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (264 µL, 0.45 mmol) and vinyl boronic ester **425a** (77.5 mg, 0.30 mmol) in pentane (600 µL), lithiation time = 1 h. The reaction mixture was stirred at 40 °C for 20 h. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 85:15) gave vinyl silane **443r** (46.0 mg, 67%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 7.8 Hz, 2H, H-2), 7.21-7.16 (m, 3H, H-1, H-3), 5.75 (d, *J* = 2.9 Hz, 1H, H-11a), 5.46 (d, *J* = 2.9 Hz, 1H, H-11b), 4.88 (br. s, 1H, H-10a), 4.84 (br. s, 1H, H-10b), 2.75-2.69 (m, 2H, H-5), 2.52-2.46 (m, 2H, H-6), 0.17 (s, 9H, H-9) ppm

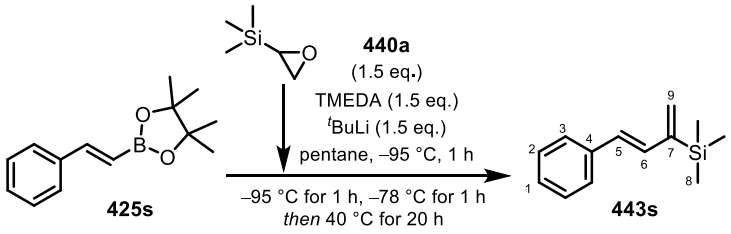
^{13}C NMR (101 MHz, $CDCl_3$): 153.0 (C), 151.2 (C), 142.4 (C), 128.5 (2 × CH), 128.4 (2 × CH), 125.9 (CH), 125.5 (CH_2), 111.9 (CH_2), 37.7 (CH_2), 34.8 (CH_2), –0.5 (3 × CH_3) ppm

IR (neat): 2952, 1454, 1248, 834, 696 cm^{-1}

HRMS (APCI) calculated for $C_{15}H_{23}Si$: 233.1564, found 233.1564

R_f = 0.84 (Pentane:CH_2Cl_2 = 85:15)

(*E*)-Trimethyl(4-phenylbuta-1,3-dien-2-yl)silane (443s)



According to **GP7** using TMEDA (68 µL, 0.45 mmol), epoxysilane **440a** (62 µL, 0.45 mmol). pentane (3.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (264 µL, 0.45 mmol) and vinyl boronic ester **425s** (77.5 mg, 0.30 mmol) in pentane (600 µL), lithiation time = 1 h. The reaction mixture was stirred at 40 °C for 20 h. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 85:15) gave vinyl silane **443s** (46.0 mg, 76%) as a colourless oil.

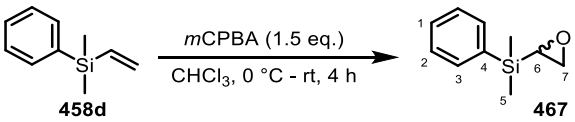
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 7.6 Hz, 2H, H-3), 7.32 (dd, J_1 = 7.6 Hz, J_2 = 7.0 Hz, 2H, H-2), 7.22 (t, J = 7.0 Hz, 1H, H-1), 6.92 (d, J = 16.3 Hz, 1H, H-6), 6.61 (d, J = 16.3 Hz, 1H, H-5), 5.86 (br.s, 1H, H-9a), 5.50 (br.s, 1H, H-9b), 0.25 (s, 9H, H-8) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 149.0 (C), 137.8 (C), 134.2 (CH), 130.7 (CH), 128.8 (CH_2), 128.7 (2 × CH), 127.5 (CH), 126.4 (2 × CH), –0.5 (3 × CH_3) ppm

R_f = 0.80 (Pentane:CH_2Cl_2 = 85:15)

Data in accordance with that reported in the literature.[217]

Dimethyl(oxiran-2-yl)(phenyl)silane (**467**)



458d 467

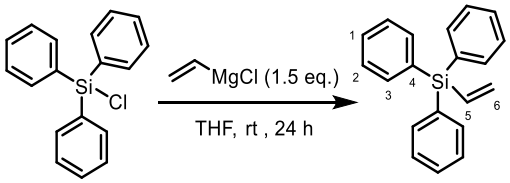
Prepared in accordance with Tanino *et al*.[218]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.53 (m, 2H, H-3), 7.43-7.35 (m, 3H, H-1 and H-2), 2.93 (dd, J_1 = 6.0 Hz, J_2 = 5.7 Hz, 1H, H-7a), 2.56 (dd, J_1 = 6.0 Hz, J_2 = 4.1 Hz, 1H, H-7b), 2.38 (dd, J_1 = 5.7 Hz, J_2 = 4.1 Hz, 1H, H-6), 0.36 (s, 3H, H-5a), 0.30 (s, 3H, H-5b) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 136.1 (C), 134.1 (2 × CH), 129.7 (CH), 128.1 (2 × CH), 44.8 (CH_2), 43.7 (CH), –5.1 (CH_3), –5.5 (CH_3) ppm

Data in accordance with that reported in the literature.[218]

Triphenyl(vinyl)silane (458e)



468 **458e**

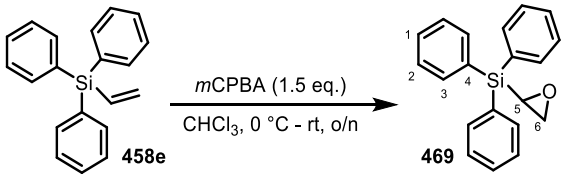
Prepared in accordance with Doye *et al*.[219]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.50 (m, 6H, H-3), 7.43-7.34 (m, 9H, H-1 and H-2), 6.70 (dd, J_1 = 18.6 Hz, J_2 = 14.6 Hz, 1H, H-5), 6.32 (dd, J_1 = 14.6 Hz, J_2 = 3.6 Hz, 1H, H-6a), 2.38 (dd, J_1 = 18.6 Hz, J_2 = 3.6 Hz, 1H, H-6b) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 137.0 (CH_2), 136.1 (6 × CH), 134.3 (3 × C), 134.0 (CH), 129.7 (3 × CH), 128.0 (6 × CH) ppm

Data in accordance with that reported in the literature.[219]

Oxiran-2-yltriphenylsilane (469)



To a solution of vinyl silane **458e** (1.25 g, 4.40 mmol) in $CHCl_3$ (2.00 mL) at 0 °C was added a suspension of *m*CPBA (1.48 g, 6.60 mmol) in $CHCl_3$ (9 mL). The reaction mixture was allowed to warm to rt and stirred vigorously overnight. The reaction was quenched with sat. $NaHCO_{3(aq)}$ (10 mL) and the phases were separated. The organic layer was washed with sat. $NaHCO_{3(aq)}$ (4 × 10 mL), dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 70:30) gave epoxysilane **469** (676 mg, 51%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 6H, H-3), 7.45 (tt, J_1 = 7.4 Hz, J_2 = 1.5 Hz, 3H, H-1), 7.39 (dd, J_1 = 8.1 Hz, J_2 = 7.4 Hz, 6H, H-2), 3.06 (dd, 1H, J_1 = 6.0 Hz, J_2 = 5.4 Hz, 1H, H-6a), 2.94 (dd, J_1 = 5.4 Hz, J_2 = 4.0 Hz, 1H, H-5), 2.56 (dd, J_1 = 6.0 Hz, J_2 = 4.0 Hz, 1H, H-6b) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 136.1 (6 × CH), 132.2 (3 × C), 130.2 (3 × CH), 128.2 (6 × CH), 44.9 (CH_2), 42.2 (CH) ppm

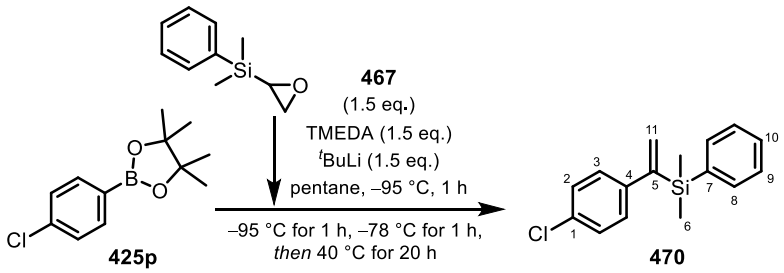
IR (neat): 1427, 1112, 711, 698 cm^{-1}

HRMS (EI) calculated for $C_{20}H_{18}OSi$: 301.1043, found 301.1042

M.P. 77 °C - 78 °C (CH_2Cl_2)

R_f = 0.43 (Pentane:CH_2Cl_2 = 50:50)

(1-(4-Chlorophenyl)vinyl)dimethyl(phenyl)silane (470)



According to **GP7** using TMEDA (68 µL, 0.45 mmol), epoxysilane **467** (80.1 mg, 0.45 mmol). pentane (3.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (264 µL, 0.45 mmol) and *p*-chlorophenyl boronic ester **425p** (71.4 mg, 0.30 mmol) in pentane (600 µL). The reaction mixture was stirred at 40 °C for 20 h. Purification of the crude residue by flash column chromatography (Pentane) gave vinyl silane **470** (31.5 mg, 39%) as a colourless oil. *Note: vinyl boronic ester* **432p** *was observed in 44% NMR yield – CH_2Br_2 was used as internal standard*

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.51 (m, 2H, H-8), 7.40-7.33 (m, 3H, H-9 and H-10), 7.19 (d, *J* = 8.5 Hz, 2H, H-2), 7.03 (d, *J* = 8.5 Hz, 2H, H-3), 5.97 (d, *J* = 2.7 Hz, 1H, H-11a), 5.69 (d, *J* = 2.7 Hz, 1H, H-11b), 0.41 (s, 6H, H-6) ppm

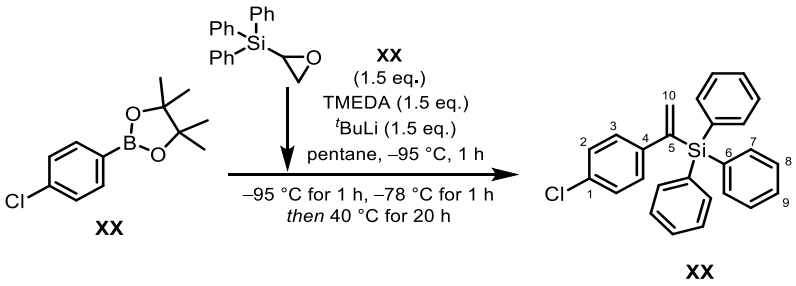
^{13}C NMR (101 MHz, $CDCl_3$): 150.2 (C), 142.8 (C), 138.0 (C), 134.1 (2 × CH), 132.4 (C), 129.7 (CH_2), 129.4 (CH), 128.4 (2 × CH), 128.3 (2 × CH), 128.1 (2 × CH), –2.3 (2 × CH_3) ppm

IR (neat): 3065, 2957, 1487, 1249, 1014, 845, 775, 698 cm^{-1}

HRMS (EI) calculated for $C_{16}H_{17}{}^{35}ClSi$: 272.0783, found 272.0783

R_f = 0.24 (Pentane)

(1-(4-Chlorophenyl)vinyl)triphenylsilane (**471**)



According to **GP7** using TMEDA (68 µL, 0.45 mmol), epoxysilane **469** (129 mg, 0.45 mmol). pentane (3.00 mL, 0.15 M w.r.t epoxide), ^{t}BuLi (264 µL, 0.45 mmol) and *p*-chlorophenyl boronic ester **425p** (71.4 mg, 0.30 mmol) in pentane (600 µL). The reaction mixture was stirred at 40 °C for 20 h. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 96:4) gave vinyl silane **471** (17.4 mg, 15%) as a white solid.

Note: vinyl boronic ester **432p** *was observed in 7% NMR yield – CH_2Br_2 was used as internal standard*

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 6H, H-7), 7.42 (tt, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 3H, H-9), 7.34 (dd, J_1 = 8.1 Hz, J_2 = 7.5 Hz, 6H, H-8), 7.14 (d, J = 8.6 Hz, 2H, H-2), 7.10 (d, J = 8.6 Hz, 2H, H-3), 6.26 (d, J = 2.6 Hz, 1H, H-10a), 5.71 (d, J = 2.6 Hz, 1H, H-10b) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 146.5 (C), 142.5 (C), 136.5 (6 × CH), 134.5 (CH_2), 134.0 (3 × C), 132.8 (C), 129.3 (3 × CH), 128.9 (2 × CH), 128.4 (2 × CH), 128.1 (6 × CH) ppm

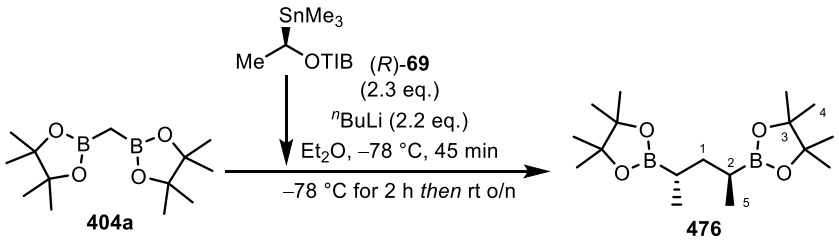
IR (neat): 3056, 1484, 1427, 1106, 838, 698 cm^{-1}

HRMS (MALDI) calculated for $C_{26}H_{21}{}^{35}ClSiNa$: 419.0999, found 419.0993

M.P. 110-111 °C (CH_2Cl_2)

R_f = 0.08 (Pentane:CH_2Cl_2 = 98:2)

2,2'-((2*S*, 4*S*)-Pentane-2,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (**476**)



To a stirred suspension of stannane (*R*)-**69** (2.53 g, 5.75 mmol) in Et_2O (25 mL) at –78 °C was added ^{n}BuLi (1.6 M in hexanes, 3.44 mL, 5.50 mmol) dropwise. The mixture was stirred for 45 min, at which point a solution of bis-boronic ester **404a** (670 mg, 2.50 mmol) in Et_2O (10 mL) was added dropwise. The resulting mixture was stirred for 2 h, at which point the cooling bath was removed and the reaction was allowed to reach rt and stirred overnight. The reaction mixture was diluted with H_2O (40 mL) and Et_2O (40 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:Et_2O = 100:0 → 95:5) gave homologated boronic ester **476** (670 mg, 83%, d.r. >95:5) as a colourless oil.

$[\alpha]^{22}_D$: + 7 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.8 Hz, 2H, H-1), 1.23 (s, 24H, H-4), 1.07 (tq, J_1 = 7.8 Hz, J_2 = 7.3 Hz, 2H, H-2), 0.93 (d, *J* = 7.3 Hz, 6H, H-5) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 82.8 (4 × C), 36.2 (CH_2), 24.9 (8 × CH_3), 15.9 (2 × CH), 15.5 (2 × CH_3) ppm

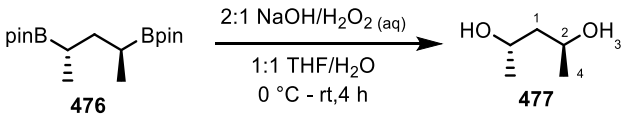
^{11}B NMR (96 MHz): 33.8 ppm

IR (neat): 2978, 1460, 1379, 1311, 1142, 968, 861 cm^{-1}

HRMS (ESI) calculated for $C_{17}H_{34}B_2O_4Na$: 347.2542, found 347.2544

R_f = 0.18 (Pentane:Et_2O = 95:5)

(2*S*,4*S*)-pentane-2,4-diol (477)



To diboronic ester **476** (65 mg, 0.20 mmol) in THF/H_2O (1:1, 2.00 mL) at 0 °C was added a pre-stirred (~2 min) mixture of 2 M $NaOH_{(aq)}$/ 30% $H_2O_{2(aq)}$ (2:1, 1.50 mL). The mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was diluted in 17% sodium $sulphate_{(aq)}$ (4 mL) and EtOAc (4 mL). The phases were separated and the aqueous phase was extracted with EtOAc (5 × 4 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:EtOAc = 100:0 → 25:75) gave diol **477** (8.9 mg, 43%) as a white amorphous solid.

$[\alpha]^{22}_D$: + 11 ° (*c* 0.27, $CHCl_3$); Lit. + 41.2 ° (*c* 1.64, $CHCl_3$) [220]

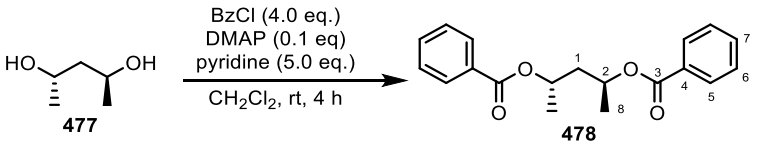
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21-4.12 (m, 2H, H-2), 2.25 (br. s, 2H, H-3), 1.61 (t, *J* = 5.5 Hz, 2H, H-1), 1.25 (d, *J* = 7.3 Hz, 6H, H-4) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 65.5 (2 × CH), 45.8 (CH_2), 23.6 (2 × CH_3) ppm

R_f = 0.16 (Pentane:EtOAc = 25:75)

Data in accordance with that reported in the literature.[221]

(2*S*,4*S*)-pentane-2,4-diyl dibenzoate (**478**)



To a solution of diol **477** (8.90 mg, 86.0 µmol), DMAP (0.10 mg, 8.60 µmol) and pyridine (35.0 µL, 0.43 mmol) in CH_2Cl_2 (1.00 mL) at rt was added benzoyl chloride (40.0 µL, 0.34 mmol) and the mixture was stirred for 4 h at room temeprature. The mixture was diluted in CH_2Cl_2 (2 mL) and H_2O (2 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 2 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash chromatography (100% CH_2Cl_2) gave bis-benzoate **478** (19.3 mg, 72%) as a colourless oil.

$[\alpha]^{22}_D$: + 47 ° (c 0.51, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.8 Hz, 4H, H-5), 7.50 (t, *J* = 7.5 Hz, 2H, H-7), 7.38 (dd, J_1 = 7.8 Hz, J_2 = 7.5 Hz, 4H, H-6), 5.32 (tq, J_1 = 6.2 Hz, J_2 = 6.2 Hz, 2H, H-2), 2.10 (t, *J* = 6.4 Hz, 2H, H-1), 1.41 (d, *J* = 6.4 Hz, 6H, H-8) ppm

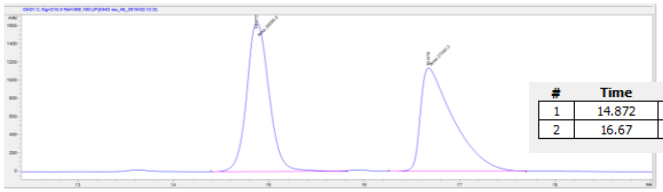
^{13}C NMR (101 MHz, $CDCl_3$): 166.1 (2 × CO), 132.9 (2 × CH), 130.7 (2 × C), 129.7 (4 × CH), 128.4 (4 × CH), 68.5 (2 × CH), 42.5 (CH_2), 20.7 (2 × CH_3) ppm

IR (neat): 2959, 1687, 1435, 1285, 1048, 770 cm^{-1}

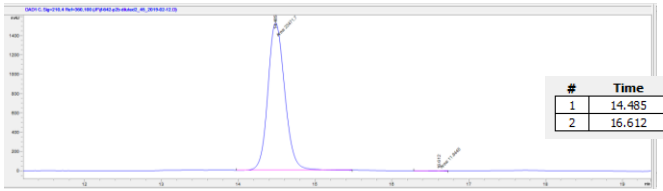
HRMS (ESI) calculated for $C_{19}H_{21}O_4$: 313.1434, found 313.1429

R_f = 0.15 (CH_2Cl_2)

Chiral HPLC: (Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 98:2, 0.5 mL/min, room temperature, 210.8 nm): tR = 14.9 minutes (maj), 16.7 minutes (min), e.r. >99:1



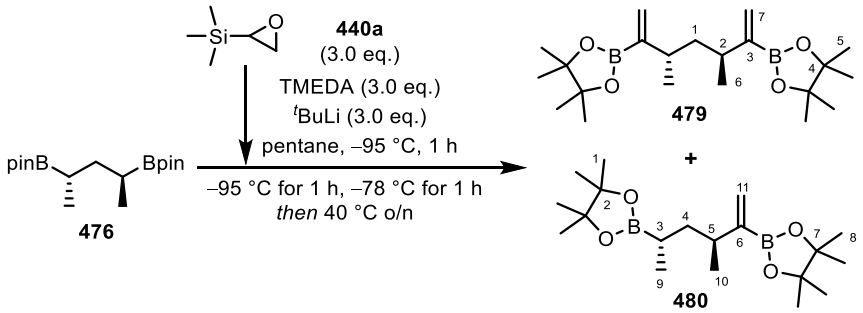
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.872	MM	26595.5	1636.1	0.2709	49.585	0.801
2	16.67	MM	27040.3	1132.4	0.398	50.415	0.313



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.485	MM	23471.7	1532.8	0.2552	99.949	0.814
2	16.612	MM	11.9	1.1	0.181	0.051	4.193

Rac-**478** was obtained by benzoylation of racemic diol *rac*-**477** using the procedure described above. *Rac*-**477** was obtained by purification of commercial 3,5-pentanediol (Sigma Aldrich) by flash chromatography (Pentane:EtOAc = 100:0 → 25:75)

2,2'-((3*S*, 5*S*)-3,5-Dimethylhepta-1,6-diene-2,6-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (479) and 2,2'-((3*S*, 5*S*)-3-methylhex-1-ene-2,5-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (480)



To a solution of TMEDA (454 µL, 3.00 mmol) and epoxysilane **440a** (420 µL, 3.00 mmol) in pentane (20.0 mL, 0.15 M w.r.t epoxide) at –95 °C (liquid N_2/MeOH) was added ^{t}BuLi (1.70 M in pentane, 1.93 mL, 3.00 mmol) dropwise (0.1 mL/min). The reaction mixture was stirred for 1 h, after which a solution of diboronic ester **476** (324 mg, 1.00 mmol) in pentane (4.00 mL) was added dropwise. The reaction mixture was stirred for 1 h, at which point the cooling bath was removed and quickly replaced with a –78 °C bath (dry ice/acetone) and stirred for an additional 1 h. The cooling bath was removed and the reaction vessel was warmed to rt, at which point it was placed in a 40 °C oil bath and stirred overnight. The reaction was cooled to rt and diluted with sat. $NH_4Cl_{(aq)}$ (15 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:Et_2O = 100:0 → 97.5:2.5) gave bis-vinylboronic ester **479** (219 mg, 58%) as a white crystalline solid and mono-vinyl boronic ester **480** (32 mg, 9%) as a colourless oil.

Bis-vinyl boronic ester **479**

[α]$^{22}_D$: – 20 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 (d, *J* = 3.3 Hz, 2H, H-7a), 5.52 (br. d, *J* = 3.3 Hz, 2H, H-7b), 1.42 (tq, J_1 = 7.2 Hz, J_2 = 6.9 Hz, 2H, H-2), 1.49 (t, *J* = 7.2 Hz, 2H, H-1), 1.25 (s, 24H, H-5), 0.93 (d, *J* = 6.9 Hz, 6H, H-6) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 127.3 (2 × CH_2), 83.1 (4 × C), 42.4 (CH_2), 37.9 (2 × CH), 24.9 (8 × CH_3), 20.8 (2 × CH_3) ppm *(Carbon attached to boron not observed due to quadrupolar relaxation)*

^{11}B NMR (96 MHz): 30.6 ppm

IR (neat): 2976, 1356, 1300, 1142, 948, 841, 695 cm^{-1}

HRMS (ESI) calculated for $C_{21}H_{38}B_2O_4Na$: 399.2856, found 399.2861

M.P. 76-78 °C (MeCN)

R_f = 0.38 (Pentane:Et_2O = 95:5)

Vinyl boronic ester **480**

$[\alpha]^{22}_D$: + 7 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (d, *J* = 3.4 Hz, 1H, H-11a), 5.55 (br. d, *J* = 3.4 Hz, 1H, H-11b), 2.35 (tq, J_1 = 7.3 Hz, J_2 = 6.8 Hz, 1H, H-5), 1.46 (t, *J* = 7.3 Hz, 2H, H-4), 1.25 (s, 12H, H-1 or H-8), 1.23 (s, 12H, H-1 or H-8), 1.01 (t, *J* = 6.8 Hz, 3H, H-10), 0.96 (m, 1H, H-3), 0.93 (d, *J* = 6.8 Hz, 3H, H-9) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 127.4 (C), 83.1 (2 × C), 82.8 (2 × C), 39.7 (CH_2), 39.0 (CH), 24.9 (8 × CH_3), 20.7 (CH_3), 16.1 (CH_3) ppm *(Both carbon atoms attached to boron are not observed due to quadrupolar relaxation)*

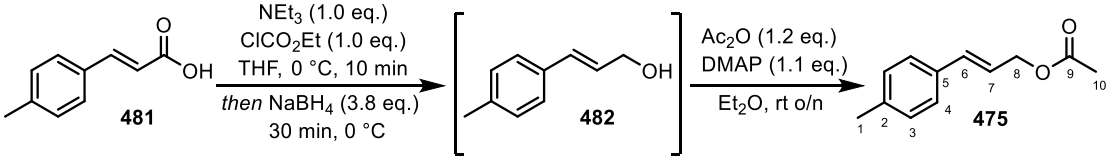
^{11}B NMR (96 MHz): 33.9, 30.3 ppm

IR (neat): 2977, 1370, 1306, 1142, 967, 750 cm^{-1}

HRMS (MALDI) calculated for $C_{19}H_{36}B_2O_4Na$: 373.2699, found 373.2691

R_f = 0.24 (Pentane:Et_2O = 95:5)

(*E*)-3-(*p*-Tolyl)allyl acetate (475)



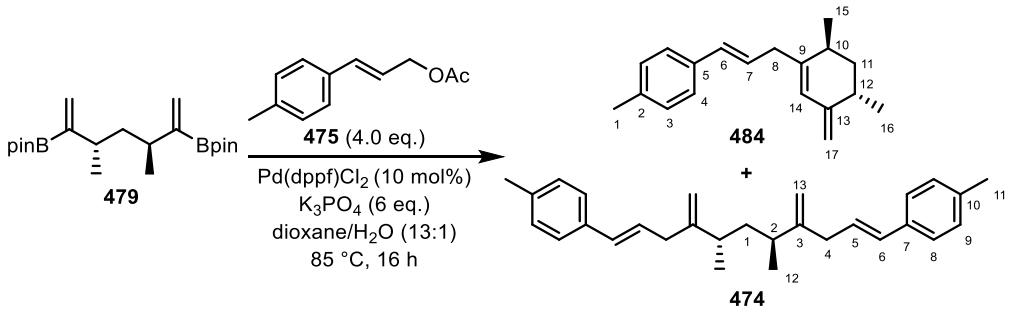
Prepared in accordance with Breder *et al*.[175]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (br. d, J = 8.0 Hz, 2H, H-4), 7.13 (d, J = 8.0 Hz, 2H, H-3), 6.62 (d, J = 15.8 Hz, 1H, H-6), 6.23 (dt, J_1 = 15.8 Hz, J_2 = 6.5 Hz, 1H, H-7), 4.72 (dd, J_1 = 6.5 Hz, J_2 = 1.1 Hz, 2H, H-8), 2.34 (s, 3H, H-1), 2.10 (s, 3H, H-10) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 170.9 (CO), 138.1 (C), 134.4 (CH), 133.5 (C), 129.4 (2 × CH), 126.6 (2 × CH), 122.2 (CH), 65.3 (CH_2), 21.3 (CH_3), 21.1 (CH_3) ppm

Data in accordance with that reported in the literature.[175]

4,4'-((1*E*, 5*S*, 7*S*, 10*E*)-5,7-Dimethyl-4,8-dimethyleneundeca-1,10-diene-1,11-diyl)bis(methylbenzene) (474) and 1-((*E*)-3-((4*S*, 6*S*)-4,6-dimethyl-3-methylenecyclohex-1-en-1-yl)prop-1-en-1-yl)-4-methylbenzene (484)



A Schlenk tube was charged with $Pd(dppf)Cl_2$ (41.0 mg, 0.01 mmol), K_3PO_4 (640 mg, 3.00 mmol), allylic acetate **475** (380 mg, 2.00 mmol), degassed 1,4-dioxane (10.0 mL, degassed for 10 min with N_2) and degassed H_2O (960 µL, degassed for 10 min with N_2). The vessel was placed in an oil bath and heated to 85 °C. Vinyl boronic ester **479** (188 mg, 0.50 mmol) in degassed 1,4-dioxane (2.50 mL) was then added in two portions over 1 h and the reaction mixture was stirred at 85 °C for 16 h. The mixture was allowed to cool to rt and filtered through a celite pad (~3 cm), the filter cake was washed with EtOAc (2 × 15 mL). The filtrate was washed with H_2O (2 × 15 mL), brine (15 mL), dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 98:2) gave triene **484** (22.5 mg, 18%, >98:2 *E/Z*) as a colourless oil and tetraene **474** (133 mg, 69%, >98:2 *E/Z*) as a colourless oil.

Triene **484**

$[\alpha]^{22}_D$: – 113 ° (*c* 0.5, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.0 Hz, 2H, H-4), 7.12 (d, *J* = 8.0 Hz, 2H, H-3), 6.38 (br. d, *J* = 15.6 Hz, 1H, H-6), 6.15 (dt, J_1 = 15.6 Hz, J_2 = 7.0 Hz, 1H, H-7), 5.93 (br. s, 1H, H-14), 4.77 (br. d, *J* = 2.0 Hz, 1H, H-7a), 4.76 (br. d, *J* = 2.0 Hz, 1H, H-7b), 2.96 (br. d, *J* = 7.0 Hz, 2H, H-8), 2.47 (m, 1H, H-12), 2.33 (s, 3H, H-1), 2.32 (m, 1H, H-10), 1.57-1.50 (m, 2H, H-11), 1.12 (d, *J* = 6.8 Hz, 3H, H-15 or H-16), 1.11 (d, *J* = 7.1 Hz, 3H, H-15 or H-16) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 149.0 (C), 144.6 (C), 136.9 (C), 135.0 (C), 131.5 (CH), 129.3 (2 × CH), 127.3 (CH), 126.1 (2 × CH), 125.6 (CH), 108.3 (CH_2), 39.4 (CH_2), 38.9 (CH_2), 31.5 (CH), 29.6 (CH), 21.3 (CH_3), 19.3 (CH_3), 19.0 (CH_3) ppm

IR (neat): 2959, 2916, 2871, 1512, 1456, 1300, 1142, 965, 885 cm^{-1}

HRMS (APCI) calculated for $C_{19}H_{25}$: 253.1951, found 253.1955

R_f = 0.55 (Pentane:CH_2Cl_2 = 95:5)

Tetraene **474**

$[\alpha]^{22}_D$: + 28 ° (*c* 1.0, $CHCl_3$)

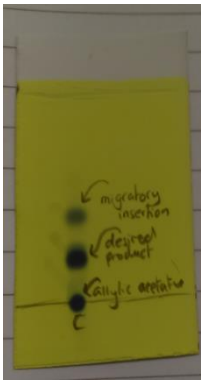
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.0 Hz, 4H, H-8), 7.10 (d, *J* = 8.0 Hz, 4H, H-9), 6.36 (d, *J* = 15.8 Hz, 2H, H-6), 6.15 (dt, J_1 = 15.8 Hz, J_2 = 7.0 Hz, 2H, H-5), 4.81 (br. s, 2H, H-13a), 4.79 (d, *J* = 1.3 Hz, 2H, H-13b), 2.88 (d, *J* = 7.0 Hz, 4H, H-4), 2.33 (s, 6H, H-11), 2.25 (tq, J_1 = 7.1 Hz, J_2 = 6.8 Hz, 2H, H-2), 1.48 (t, *J* = 7.1 Hz, 2H, H-1), 1.03 (d, *J* = 6.8 Hz, 6H, H-10) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 153.4 (2 × C), 136.8 (2 × C), 135.1 (2 × C), 131.3 (2 × CH), 129.3 (4 × CH), 127.9 (2 × CH), 126.1 (4 × CH), 109.7 (2 × CH_2), 41.5 (CH_2), 37.8 (2 × CH), 37.5 (2 × CH_2), 21.3 (2 × CH_3), 20.6 (2 × CH_3) ppm

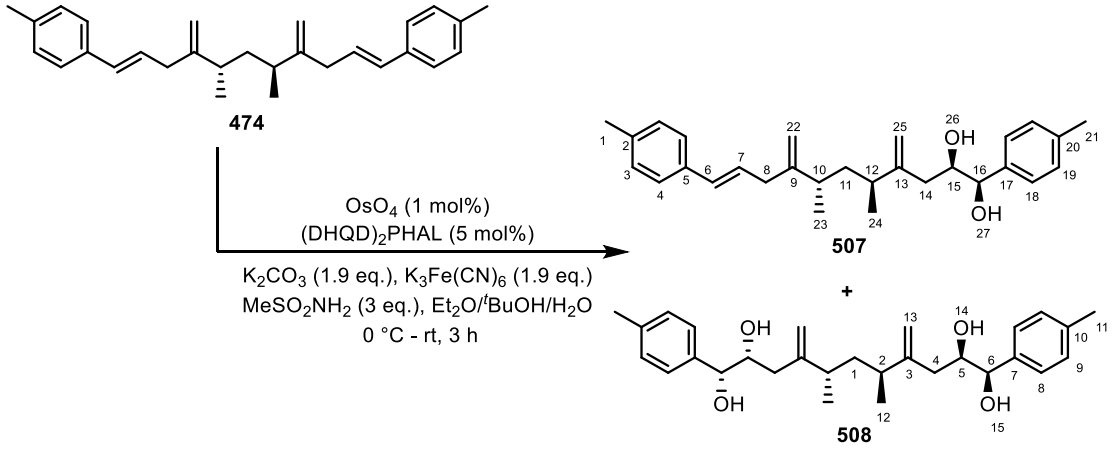
IR (neat): 2978, 1371, 1311, 1142, 967, 861 cm^{-1}

HRMS (MALDI) calculated for $C_{29}H_{36}Na$: 407.2709, found 407.2714

R_f = 0.36 (Pentane:CH_2Cl_2 = 95:5)



(1*R*, 2*R*, 5*S*, 7*S*, *E*)-5,7-Dimethyl-4,8-dimethylene-1,11-di-*p*-tolylundec-10-ene-1,2-diol (**507**) **and (1*R*, 2*R*, 5*S*, 7*S*, 9*S*, 10*S*)-5,7-dimethyl-4,8-dimethylene-1,11-di-*p*-tolylundecane-1,2,9,10-tetraol** (**508**)



OsO_4 (2.5% in ^{t}BuOH, 33.0 µL, 3.20 µM) was added to a mixture of $K_3Fe(CN)_6$ (200 mg, 0.61 mmol), K_2CO_3 (84.3 mg, 0.61 mmol), $(DHQD)_2PHAL$ (12.5 mg, 16.0 µM) and methanesulfonamide (91.2 mg, 0.96 mmol) in ^{t}BuOH/H_2O (1:1, v/v, 1.60 mL) at rt. The mixture was cooled to 0 °C, which caused a solid to precipitate, and tetraene **474** (123 mg, 0.32 mmol) in Et_2O (200 µL) was added in one portion. The reaction mixture was warmed to rt and stirred for 3 h, at which point sodium sulfite (500 mg) was added and the mixture was stirred an additional 30 min. The product was extracted with EtOAc (5 × 2 mL) and the combined organic extracts were washed with 2 N $KOH_{(aq)}$ (2 × 3 mL), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:EtOAc = 100:0 → 88:12) gave recovered tetraene **474** (45.5 mg, 37%) as a yellow oil and diol **507** (45.5 mg, 34%, d.r. >95:5) as a colourless oil. Further elution (Pentane:EtOAc = 88:12 → 50:50) gave tetraol **508** (18.8 mg, 13%, d.r. >95:5) as a colourless oil.

Diol **507**

$[\alpha]^{22}_D$: – 22 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.22 (m, 4H, H-4 and H-18), 7.16 (d, J = 8.0 Hz, 2H, H-19), 7.11 (d, J = 8.0 Hz, 2H, H-3), 6.35 (br. d, J = 15.6 Hz, 1H, H-6), 6.13 (dt, J_1 = 15.8 Hz, J_2 = 7.1 Hz, 1H, H-7), 4.90 (br. s, 1H, H-25a), 4.86 (br. d, J = 1.1 Hz, 1H, H-25b), 4.79-4.76 (m, 2H, H-22), 4.46 (dd, J_1 = 6.4 Hz, J_2 = 3.7 Hz, 1H, H-16), 3.84 (m, 1H, H-15), 2.85 (br. d, J = 7.1 Hz, 2H, H-8), 2.73 (d, J = 3.8 Hz, 1H, H-27), 2.34 (s, 3H, H-1 or H-21), 2.33 (s, 3H, H-1 or H-21), 2.26 (d, J = 2.9 Hz, 1H, H-26), 2.19 (tq, J_1 = 7.1

Hz, J_2 = 6.9 Hz, 1H, H-10), 2.13-2.04 (m, 3H, H-12 and H-14), 1.46-1.32 (m, 2H, H-11), 0.99 (d, J = 6.9 Hz, 3H, H-23), 0.89 (d, J = 6.9 Hz, 3H, H-24) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 153.2 (C), 151.2 (C), 138.1 (C), 137.9 (C), 136.8 (C), 135.0 (C), 131.4 (CH), 129.3 (4 × CH), 127.8 (CH), 126.9 (2 × CH), 126.1 (2 × CH), 110.9 (CH_2), 109.8 (CH_2), 77.5 (CH), 73.8 (CH), 41.1 (CH_2), 38.2 (CH_2), 37.8 (CH), 37.6 (CH), 37.3 (CH_2), 21.3 (2 × CH_3), 20.7 (CH_3), 20.5 (CH_3) ppm

IR (neat): 3392 (br.), 2957, 2921, 1640, 1513, 1455, 1057, 968, 892, 817 cm^{-1}

HRMS (MALDI) calculated for $C_{29}H_{38}O_2Na$: 441.2764, found 441.277

R_f = 0.45 (Pentane:EtOAc = 70:30)

Note: We found the commercial AD-mix to be less effective than that prepared in house

Tetraol **508**

$[\alpha]^{22}_D$: – 28 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 8.1 Hz, 4H, H-8), 7.16 (d, J = 8.1 Hz, 4H, H-9), 4.84 (br. s, 4H, H-13), 4.44 (dd, J_1 = 6.2 Hz, J_2 = 2.3 Hz, 2H, H-6), 3.86-3.79 (m, 2H, H-5), 2.79 (br. s, 2H, H-15), 2.48 (br. s, 2H, H-14), 2.34 (s, 6H, H-11), 2.12-2.00 (m, 6H, H-2 and H-4), 1.38 (t, J = 7.2 Hz, 2H, H-1), 0.85 (d, J = 6.9 Hz, 6H, H-12) ppm

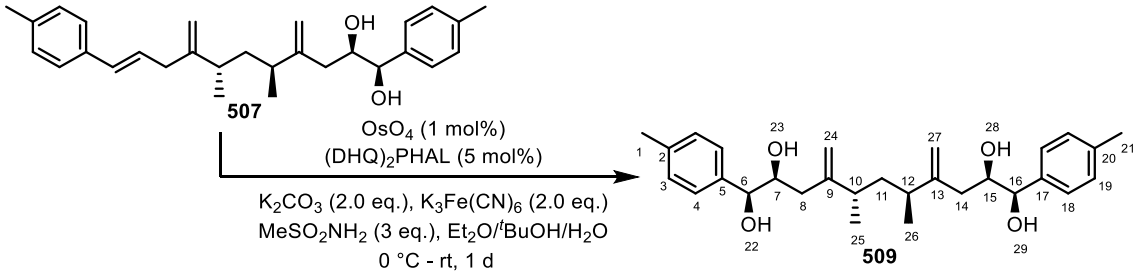
^{13}C NMR (101 MHz, $CDCl_3$): 150.9 (2 × C), 138.1 (2 × C), 137.8 (2 × C), 129.3 (4 × CH), 126.9 (4 × CH), 110.7 (2 × CH_2), 77.5 (2 × CH), 73.7 (2 × CH), 40.6 (CH_2), 38.5 (2 × CH_2), 36.7 (2 × CH), 21.3 (2 × CH_3), 21.1 (2 × CH_3) ppm

IR (neat): 3379 (br.), 2957, 2922, 1275, 1261, 1059, 817, 769 cm^{-1}

HRMS (MALDI) calculated for: $C_{29}H_{40}O_4Na$: 475.2819, found 475.2830

R_f = 0.38 (Pentane:EtOAc = 40:60)

(1*R*, 2*R*, 5*S*, 7*S*, 10*S*, 11*S*)-5,7-Dimethyl-4,8-dimethylene-1,11-di-*p*-tolylundecane-1,2,10,11-tetraol (509)



OsO_4 (2.5% in ^{t}BuOH, 10.0 µL, 1.00 µM) was added to a mixture of $K_3Fe(CN)_6$ (65.8 mg, 0.20 mmol), K_2CO_3 (27.6 mg, 0.20 mmol), $(DHQ)_2PHAL$ (3.90 mg, 5.00 µM) and methanesulfonamide (28.5 mg, 0.30 mmol) in ^{t}BuOH/H_2O (1:1, v/v, 600 µL) at rt. The mixture was cooled to 0 °C, which caused a solid to precipitate, and diol **507** (41.8 mg, 0.10 mmol) in Et_2O (100 µL) was added in one portion. The reaction mixture was warmed to rt and stirred for 24 h, at which point sodium sulfite (170 mg) was added and the mixture was stirred an additional 30 min. The product was extracted with EtOAc (5 × 1 mL) and the combined organic extracts were washed with 2 N $KOH_{(aq)}$ (2 × 2 mL), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:EtOAc = 100:0 → 50:50) gave recovered diol **507** (3.80 mg, 9%) as a yellow oil and tetraol **509** (41.3 mg, 91%, d.r. >95:5) as a colourless oil.

$[\alpha]^{22}_D$: – 7 ° (*c* 0.5, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.1 Hz, 4H, H-4 and H-18), 7.18-7.13 (m, 4H, H-3 and H-19), 4.86-4.83 (m, 2H, H-24a or H-27a), 4.79-4.77 (m, 2H, H-24b or H-27b), 4.45-4.40 (m, 2H, H-6 and H-16), 3.85-3.75 (m, 2H, H-7 and H-15), 2.73 (br. s, 2H, H-22 and H-29), 2.45-2.37 (m, 2H, H-23 and H-28), 2.34 (s, 3H, H-1 or H-21), 2.33 (s, 3H, H-1 or H-21), 2.10-1.96 (m, 6H, H-8, H-10, H-12 and H-14), 1.30-1.24 (m, 2H, H-11), 0.92 (t, *J* = 6.9 Hz, 3H, H-25), 0.79 (t, *J* = 6.9 Hz, 3H, H-26) ppm .

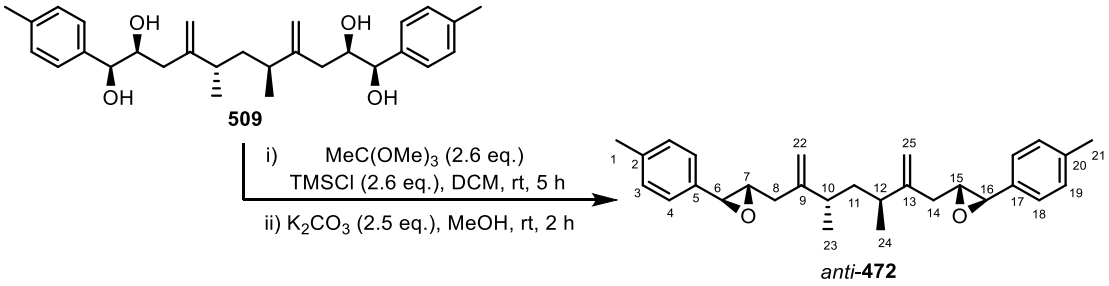
^{13}C NMR (101 MHz, $CDCl_3$): 151.4 (C), 151.1 (C), 138.2 (C), 138.1 (C), 137.9 (2 × C), 129.3 (4 × CH), 127.0 (4 × CH), 110.7 (CH_2), 110.4 (CH_2), 77.6 (CH), 77.5 (CH), 74.3 (CH), 73.7 (CH), 41.5 (CH_2), 38.4 (CH_2), 38.3 (CH_2), 37.1 (CH), 36.9 (CH), 21.3 (2 × CH_3), 20.7 (CH_3), 20.6 (CH_3) ppm

IR (neat): 3275 (br.), 2957, 2916, 1640, 1515, 1431, 1071, 1017, 968, 815, 542 cm^{-1}

HRMS (MALDI) calculated for $C_{29}H_{40}O_4Na$: 475.2819, found 475.2829

R_f = 0.19 (Pentane:EtOAc = 50:50)

(2*S*, 3*S*)-2-((3*S*, 5*S*)-3,5-dimethyl-2-methylene-6-(((2*R*, 3*R*)-3-(*p*-tolyl)oxiran-2-yl)methyl)hept-6-en-1-yl)-3-(*p*-tolyl)oxirane *anti*-(**472**)



To a Schlenk tube containing a solution of tetraol **509** (22.6 mg, 0.05 mmol) and trimethylorthoacetate (16.5 µL, 0.13 mmol) in CH_2Cl_2 (250 µL) at rt was added trimethylsilyl chloride (16.5 µL, 0.13 mmol) and the mixture was stirred at rt for 5 h. The volatiles were removed under reduced pressure (high vacuum for 10 min), after which the reaction vessel was charged with K_2CO_3 (17.3 mg, 0.13 mmol) and MeOH (600 µL). The reaction mixture was stirred vigorously at rt for 2 h and then diluted with sat. $NH_4Cl_{(aq)}$ (2 mL). The product was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 30:70) gave bis-epoxide *anti*-**472** (10.8 mg, 52%) as a colourless oil.

$[\alpha]^{22}_D$: – 6 ° (*c* 0.32, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.12 (m, 8H, H-3, H-4, H-18 and H-19), 4.90-4.86 (m, 2H, H-22 or H-25), 4.86-4.83 (m, 2H, H-22 or H-25), 3.61-3.58 (m, 2H, H-6 and H-16), 3.06 (td, J_1 = 6.1 Hz, J_2 = 2.1 Hz, 1H, H-7 or H-15), 3.04 (td, J_1 = 6.1 Hz, J_2 = 2.1 Hz, 1H, H-7 or H-15), 2.47-2.35 (m, 2H, H-8 or H-14), 2.34 (s, 6H, H-1 and H-21), 2.29-2.18 (m, 4H, H-10, H-12 and H-8 or H-14), 1.44-1.39 (m, 2H, H-11), 1.01 (t, *J* = 7.0 Hz, 6H, H-23 and H-24) ppm

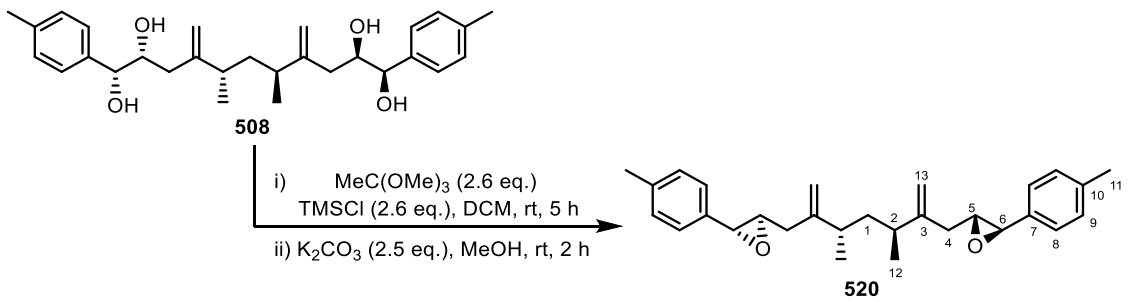
^{13}C NMR (101 MHz, $CDCl_3$): 150.1 (2 × C), 138.0 (2 × C), 134.7 (2 × C), 129.3 (4 × CH), 125.7 (4 × CH), 110.9 (CH_2), 110.8 (CH_2), 62.1 (2 × CH), 59.1 (2 × CH), 41.0 (CH_2), 38.3 (2 × CH), 36.4 (CH_2), 36.3 (CH_2), 21.3 (2 × CH_3), 20.4 (2 × CH_3) ppm

IR (neat): 2959, 2923, 1641, 1518, 1455, 1057, 893, 815 cm^{-1}

HRMS (MALDI) calculated for $C_{29}H_{36}O_2Na$: 439.2608, found 439.2615

R_f = 0.39 (Pentane:CH_2Cl_2 = 25:75)

(2*R*, 2'*R*, 3*R*, 3'*R*)-3,3'-((3*S*, 5*S*)-3,5-dimethyl-2,6-dimethyleneheptane-1,7-diyl)bis(2-(*p*-tolyl)oxirane) (**520**)



To a Schlenk tube containing a solution of tetraol **508** (19.9 mg, 44.0 µmol) and trimethylorthoacetate (14.6 µL, 0.12 mmol) in CH_2Cl_2 (250 µL) at rt was added trimethylsilyl chloride (14.6 µL, 0.12 mmol) and the mixture was stirred at rt for 2 h. The volatiles were removed under reduced pressure (high vacuum for 10 min), after which the reaction vessel was charged with K_2CO_3 (15.3 mg, 0.11 mmol) and MeOH (600 µL). The reaction mixture was stirred vigorously at rt for 3 h and then diluted with sat. $NH_4Cl_{(aq)}$ (2 mL). The product was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:CH_2Cl_2 = 100:0 → 40:60) gave bis-epoxide **520** (6.5 mg, 35%) as a colourless oil.

$[\alpha]^{22}_D$: + 6 ° (*c* 0.18, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-7.12 (m, 8H, H-8 and H-9), 4.89-4.86 (m, 2H, H-13a), 4.86-4.83 (m, 2H, H-13b), 3.50 (d, J = 2.1 Hz, 2H, H-6), 3.06 (td, J_1 = 5.9 Hz, J_2 = 1.9 Hz, 2H, H-5), 2.39 (dd, J_1 = 15.9 Hz, J_2 = 5.7 Hz, 2H, H-4a), 2.34 (s, 6H, H-11), 2.29-2.21 (m, 4H, H-2 and H-4b), 1.42 (t, J = 7.2 Hz, 2H, H-1), 1.01 (t, J = 7.0 Hz, 6H, H-12) ppm

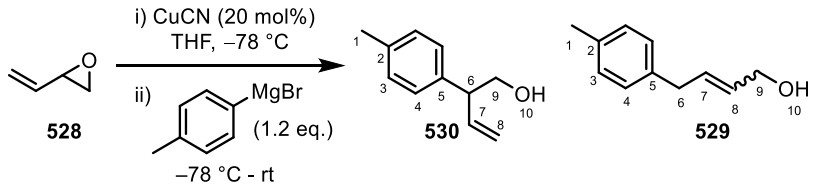
^{13}C NMR (101 MHz, $CDCl_3$): 150.0 (2 × C), 138.0 (2 × C), 134.7 (2 × C), 129.3 (4 × CH), 125.7 (4 × CH), 110.8 (2 × CH_2), 62.1 (2 × CH), 59.1 (2 × CH), 40.8 (CH_2), 38.3 (2 × CH), 36.3 (2 × CH_2), 21.3 (2 × CH_3), 20.4 (2 × CH_3) ppm

IR (neat): 2959, 2922, 1641, 1518, 1455, 953, 893, 815 cm^{-1}

HRMS (MALDI) calculated for $C_{29}H_{36}O_2Na$: 439.2608, found 439.2599

R_f = 0.41 (Pentane:CH_2Cl_2 = 25:75)

2-(*p*-Tolyl)but-3-en-1-ol (**530**) **and 4-(*p*-tolyl)but-2-en-1-ol** (**529**)



Performed according to a modified procedure from Ghosh *et al*.[190]

To a 100 mL Schlenk flask fitted with a condenser was added magnesium turnings (1.03 g, 42.5 mmol) and THF (46.0 mL). To the stirred mixture at rt was added *p*-bromotoluene (5.13 g, 30.0 mmol) dropwise and stirring was continued until reflux had ceased and the mixture had cooled to ambient temperature (*ca.* 1 h).

In a separate flask CuCN (224 mg, 7.50 mmol) was added to a solution of butadiene mono-oxide (**528**) (2.01 mL, 25.0 mmol) in THF (46.0 mL) and the resulting mixture was cooled to –78 °C. Freshly prepared *p*-tolylmagnesium bromide (1 M in THF, 3.00 mL, 3.00 mmol) was added dropwise to the mixture which was then warmed to 0 °C and stirred until a homogeneous mixture was obtained. The reaction mixture was cooled back to –78 °C and *p*-tolylmagnesium bromide (1 M in THF, 27.0 mL, 27.0 mmol) was added dropwise and the mixture was slowly allowed to reach room temperature overnight. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (25 mL), then $NH_4OH_{(aq)}$ (3 mL), H_2O (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:EtOAc = 100:0 → 85:15) gave homoallylic alcohol **530** (270 mg, 7%) as a colourless oil and allylic alcohol **529** (3.60 g, 89%, *E/Z* = 89:11) as a pale yellow oil.

Homoallylic alcohol **530**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-7.11 (m, 4H, H-3 and H-4), 5.99 (ddd, J_1 = 17.1 Hz, J_2 = 10.0 Hz, J_3 = 7.6 Hz, 1H, H-7), 5.20 (br. d, *J* = 10.0 Hz, 1H, H-8a), 5.18 (br. d, *J* = 17.1 Hz, 1H, H-8b), 3.81 (t, *J* = 6.3 Hz, 2H, H-9), 3.50 (q, *J* = 7.6 Hz, 1H, H-6), 2.33 (s, 3H, H-1), 1.44 (t, *J* = 6.3 Hz, 1H, H-10)

^{13}C NMR (101 MHz, $CDCl_3$): 138.6 (CH), 137.7 (C), 136.7 (C), 129.6 (2 × CH), 127.9 (2 × CH), 117.0 (CH_2), 66.2 (CH_2), 55.3 (CH), 21.1 (CH_3) ppm

R_f = 0.38 (Pentane:EtOAc = 80:20)

Data in accordance with that reported in the literature.[222]

Allylic alcohol **529** (Characterisation of *E*-isomer)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, *J* = 8.0 Hz, 2H, H-3), 7.07 (d, *J* = 8.0 Hz, 2H, H-4), 5.85 (dt, J_1 = 15.2 Hz, J_2 = 6.7 Hz, 1H, H-7), 5.70 (dt, J_1 = 15.2 Hz, J_2 = 5.8 Hz, 1H, H-8), 4.12 (t, *J* = 5.8 Hz, 2H, H-9), 3.35 (br. d, *J* = 6.7 Hz, 2H, H-6), 2.32 (s, 3H, H-1), 1.25 (t, *J* = 5.8 Hz, 1H, H-10) ppm

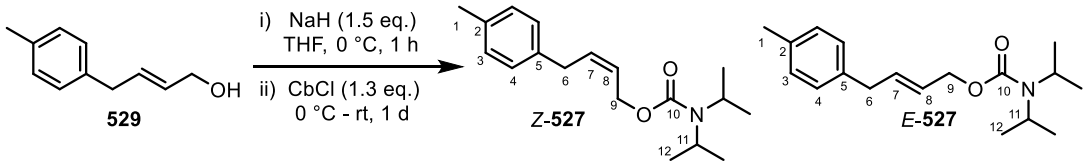
^{13}C NMR (101 MHz, $CDCl_3$): 137.1 (C), 135.8 (C), 132.1 (CH), 130.2 (CH), 129.3 (2 × CH), 128.6 (2 × CH), 63.7 (CH_2), 38.4 (CH_2), 21.1 (CH_3) ppm

IR (neat): 3317, 2920, 1514, 969, 804 cm^{-1}

HRMS (APCI) calculated for $C_{11}H_{13}$ [M+H-H_2O]: 145.1012, found 145.1010

R_f = 0.26 (Pentane:EtOAc = 80:20)

(*Z*)-4-(*p*-Tolyl)but-2-en-1-yl diisopropylcarbamate *Z*-(527) and (*E*)-4-(*p*-tolyl)but-2-en-1-yl diisopropylcarbamate *E*-(527)



To a solution of allylic alcohol **529** (2.43 g, 15.0 mmol) in THF (30 mL) at 0 °C was added sodium hydride (540 mg, 22.5 mmol) and the mixture was stirred for 30 mins, at which point *N*,*N*-diisopropylcarbamoyl chloride (3.19 g, 19.5 mmol) was added in one portion. The reaction mixture was warmed to room temperature. After 24 h, the reaction was cooled to 0 °C and quenched with sat. $NH_4Cl_{(aq)}$ (30 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:Et_2O = 100:0 → 95:5) gave (*Z*)-allylic carbamate *Z*-**527** (313 mg, 7%, >98:2 *Z/E*) as a pale yellow oil and (*E*)-allylic carbamate *E*-**527** (3.25 g, 75%, >98:2 *E/Z*) as a pale yellow oil. Futher elution (100% EtOAc) gave recovered allylic alcohol **529** (240 mg, 10%) as a yellow oil.

(*Z*)-Allylic carbamate *Z*-**527**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12-7.06 (m, 4H, H-3 and H-4), 5.76 (dt, J_1 = 11.0 Hz, J_2 = 7.5 Hz, 1H, H-7), 5.69 (dt, J_1 = 11.0 Hz, J_2 = 6.4 Hz, 1H, H-8), 4.75 (d, J = 6.4 Hz, 2H, H-9), 3.92 (br. s, 2H, H-11), 3.44 (d, J = 7.5 Hz, 2H, H-6), 2.31 (s, 3H, H-1), 1.22 (d, J = 6.9 Hz, 12H, H-12) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 155.8 (CO), 137.2 (C), 135.7 (C), 132.9 (CH), 129.3 (2 × CH), 128.4 (2 × CH), 125.4 (CH), 60.5 (CH_2), 46.0 (2 × CH), 33.5 (CH_2), 21.2 (4 × CH_3), 21.1 (CH_3) ppm

IR (neat): 2997, 2969, 1688, 1433, 1286, 1045, 970, 770 cm^{-1}

HRMS (ESI) calculated for $C_{18}H_{27}NO_2Na$: 312.1934, found 312.1928

R_f = 0.32 (Pentane:Et_2O = 90:10)

(*E*)-Allylic carbamate *E*-**527**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.1 Hz, 2H, H-3), 7.07 (d, *J* = 8.1 Hz, 2H, H-4), 5.90 (dt, J_1 = 15.3 Hz, J_2 = 6.8 Hz, 1H, H-7), 5.69 (dt, J_1 = 15.3 Hz, J_2 = 6.2 Hz, 1H, H-8), 4.56 (d, *J* = 6.2 Hz, 2H, H-9), 3.91 (br. s, 2H, H-11), 3.36 (d, *J* = 6.8 Hz, 2H, H-6), 2.32 (s, 3H, H-1), 1.21 (d, *J* = 6.6 Hz, 12H, H-12) ppm

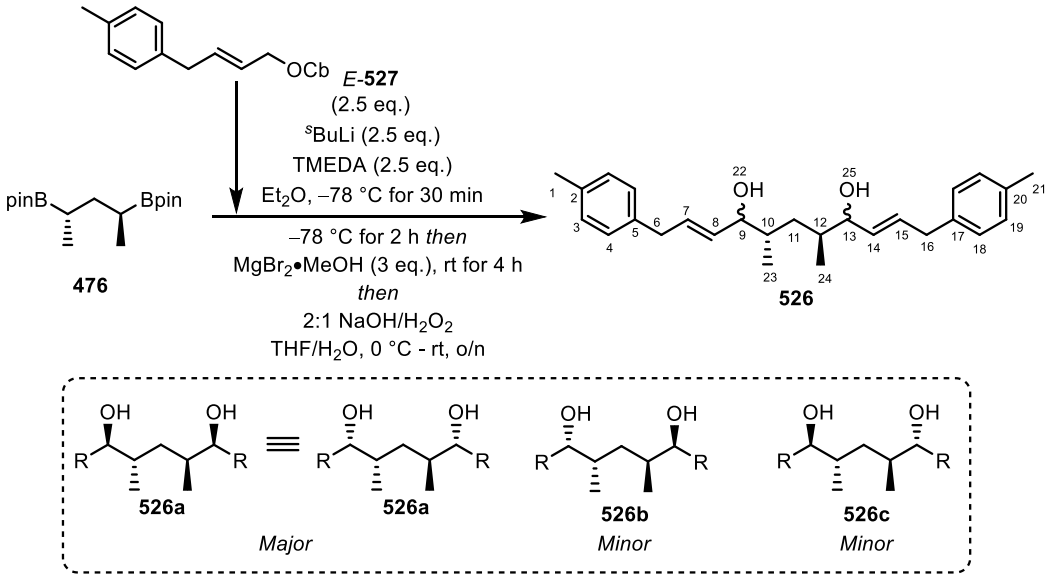
^{13}C NMR (101 MHz, $CDCl_3$): 155.6 (C), 137.0 (C), 135.8 (C), 133.5 (CH), 129.3 (2 × CH), 128.5 (2 × CH), 126.6 (CH), 65.1 (CH_2), 45.8 (2 × CH), 38.4 (CH_2), 21.2 (4 × CH_3), 21.1 (CH_3) ppm

IR (neat): 2978, 2873, 1637, 1410, 1050, 962, 765 cm^{-1}

HRMS (ESI) calculated for $C_{18}H_{27}NO_2Na$: 312.1934, found 312.1929

R_f = 0.24 (Pentane:Et_2O = 90:10)

(1*E*,5*S*,7*S*,9*E*)-5,7-Dimethyl-1,11-di-*p*-tolylundeca-1,9-diene-4,8-diol (**526**)



To a solution of allylic carbamate *E*-**527** (22.6 mg, 2.50 mmol) and TMEDA (375 µL, 2.50 mmol) in Et_2O (12.5 mL) at –78 °C was added ^{s}BuLi (1.27 M in hexanes, 1.97 mL, 2.50 mmol) dropwise (0.3 mL/min). The mixture was stirred for 45 mins, at which point diboronic ester **476** (324 mg, 1.00 mmol) in Et_2O (4 mL) was added dropwise and the mixture was stirred for 2 h at –78 °C. $MgBr_2$·MeOH (1.00 M, 3.00 mL, 3.00 mmol) was added, the cooling bath was removed and the mixture was stirred vigorously at rt for 4 h. At this stage, THF (5 mL) and H_2O (5 mL) was added and the solution was cooled to 0 °C. A pre-mixed (~ 3 min) solution of 2 M $NaOH_{(aq)}$/30% wt $H_2O_{2(aq)}$ (2:1 v/v, 4.5 mL) was added and the resulting mixture was warmed to rt and stirred overnight. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:EtOAc = 100:0 → 70:30) gave diol **526** (301 mg, 77%, d.r. 1.5:1.3:1.0) as a waxy white solid.

$[\alpha]^{22}_{D}$: – 1 ° (*c* 0.5, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.5 Hz, 4H, H-3 and H-19), 7.06 (d, *J* = 8.5 Hz, 4H, H-4 and H-18), 5.78 (dt, J_1 = 15.2 Hz, J_2 = 6.7 Hz, 2H, H-7 and H-15), 5.54 (dd, J_1 = 15.2 Hz, J_2 = 7.3 Hz, 2H, H-8 and H-14), 3.92 (br. s, 1H, H-9 or H-13), 3.88 (br. s, 1H, H-9 or H-13), 3.34 (d, *J* = 6.7 Hz, 4H, H-6 and H-16), 2.31 (s, 6H, H-1 and H-21), 1.73-1.61 (m, 2H, H-10 and H-12) 1.51 (br. s, 1H, H-22 or H-25), 1.45 (br. s, 1H, H-22 or H-25), 1.30-1.20 (m, 2H, H-11), 0.88 (d, *J* = 6.7 Hz, 3H, H-23 or H-24), 0.86 (d, *J* =

6.9 Hz, 3H, H-23 or H-24) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 137.2 (2 × C), 135.7 (2 × C), 132.5 (2 × CH), 132.4 (2 × CH), 131.9 (4 × CH), 131.8 (4 × CH), 77.6 (2 × CH), 38.5 (2 × CH_2), 36.4 (CH), 36.0 (CH), 35.1 (CH_2), 21.1 (2 × CH_3), 15.2 (CH_3), 15.0 (CH_3) ppm

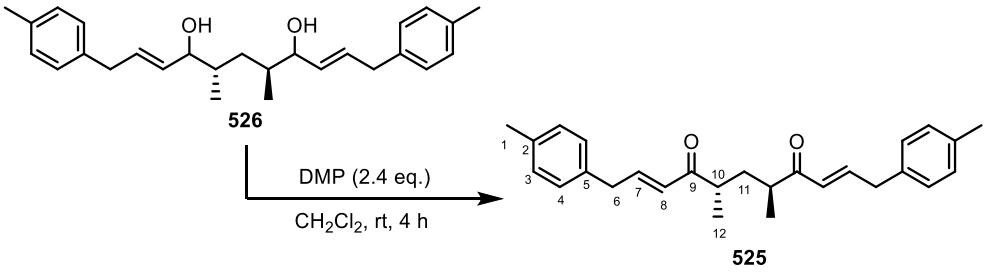
IR (neat): 3323 (br.), 2958, 2920, 1513, 1004, 963, 799 cm^{-1}

HRMS (ESI) calculated for $C_{27}H_{36}O_2Na$: 415.2608, found 415.2610

R_f = 0.15 (Pentane:EtOAc = 70:30)

Note: NMR data shown for major diastereomer **526a** *only*

(2*E*,5*S*,7*S*,9*E*)-5,7-dimethyl-1,11-di-*p*-tolylundeca-2,9-diene-4,8-dione (**525**)



To a solution of diol **526** (39.3 mg, 0.10 mmol) in CH_2Cl_2 (6 mL) at rt was added Dess-Martin Periodinane (102 mg, 0.24 mmol) and the mixture was stirred for 4 h. The reaction was quenched with sat. $NaHCO_{3\,(aq)}$ (5 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:Et_2O = 100:0 → 80:20) gave diketone **525** (37.4 mg, 100%) as a colourless oil.

$[\alpha]^{22}_D$: + 10 ° (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, *J* = 7.8 Hz, 4H, H-3), 7.02 (d, *J* = 7.8 Hz, 4H, H-4), 6.91 (dt, J_1 = 15.7 Hz, J_2 = 6.8 Hz, 2H, H-7), 5.70 (dt, J_1 = 15.7 Hz, J_2 = 1.5 Hz, 2H, H-8), 3.44 (br. d, *J* = 6.8 Hz, 4H, H-6), 2.74 (sxt, *J* = 7.2 Hz, 2H, H-10), 2.32 (s, 6H, H-1), 1.71 (t, *J* = 7.2 Hz, 2H, H-11), 1.05 (d, *J* = 6.8 Hz, 6H, H-12) ppm

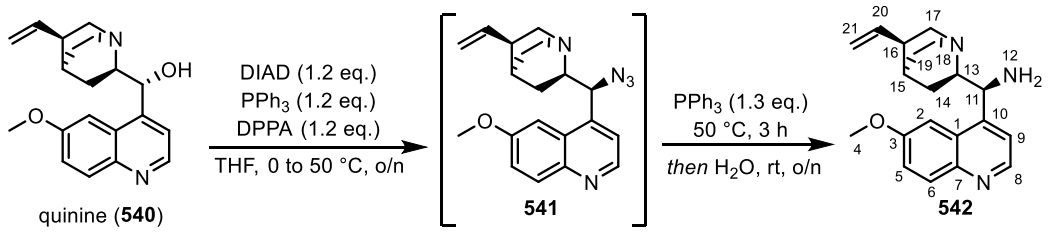
^{13}C NMR (101 MHz, $CDCl_3$): 203.7 (2 × CO), 146.1 (2 × CH), 136.4 (2 × C), 134.7 (2 × C), 129.9 (2 × CH), 129.5 (4 × CH), 128.7 (4 × CH), 41.5 (2 × CH), 38.4 (2 × CH_2), 36.2 (CH_2), 21.1 (2 × CH_3), 17.9 (2 × CH_3) ppm

IR (neat): 2957, 2920, 1685, 1638, 1625, 1485, 929, 815 cm^{-1}

HRMS (ESI) calculated for $C_{27}H_{33}O_2$: 389.2475, found 389.2469

R_f = 0.16 (Pentane:Et_2O = 90:10)

(S)-(6-Methoxyquinolin-4-yl)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methanamine (542)



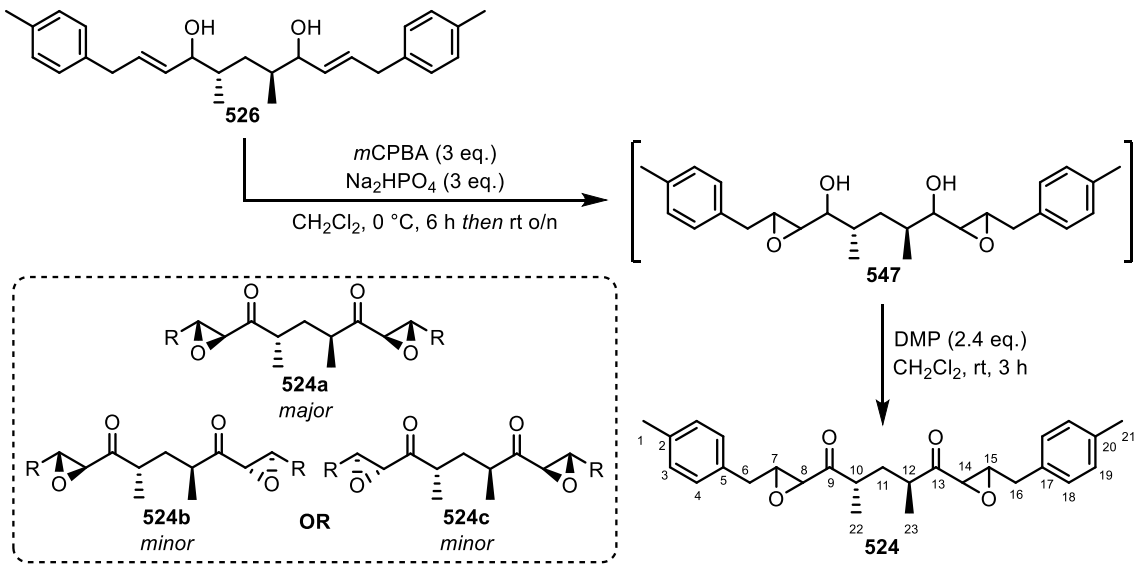
Prepared according to List *et al.*[191]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, *J* = 4.6 Hz, 1H, H-8), 8.04 (d, *J* = 9.2 Hz, 1H, H-6), 7.65 (br. s, 1H, H-2), 7.46 (br. d, *J* = 4.6 Hz, 1H, H-9), 7.39 (dd, J_1 = 9.2 Hz, J_2 = 2.7 Hz, 1H, H-5), 5.80 (ddd, J_1 = 17.3 Hz, J_2 = 10.1 Hz, J_3 = 7.3 Hz, 1H, H-20), 5.00 (dd, J_1 = 17.3 Hz, J_2 = 1.4 Hz, 1H, H-21a), 4.97 (dd, J_1 = 10.1 Hz, J_2 = 1.4 Hz, 1H, H-21b), 4.60 (br. d, *J* = 9.2 Hz, H-11), 3.97 (s, 3H, H-4), 3.29 (dd, J_1 = 12.6 Hz, J_2 = 10.1 Hz, 1H, H-17a), 3.11 (m, 1H, H-18a), 3.09 (m, 1H, H-13), 2.87-2.78 (m, 2H, H-17b and H-18b), 2.29 (m, 1H, H-16), 1.74 (br. s, 2H, H-12), 1.65-1.54 (m, 3H, H-15 and H-19), 1.43 (m, 1H, H-14a), 0.78 (m, 1H, H-14b) ppm

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.7 (C), 148.0 (CH), 147.2 (C), 144.9 (C), 141.9 (CH), 132.0 (CH), 128.9 (C), 121.3 (CH), 120.0 (CH), 114.4 (CH_2), 102.1 (CH), 61.9 (CH), 56.5 (CH_2), 55.7 (CH_3), 52.5 (CH), 41.1 (CH_2), 40.0 (CH), 28.3 (CH_2), 27.7(CH), 26.2 (CH_2) ppm

Data in accordance with that reported in the literature.[191]

(2*S*,4*S*)-2,4-dimethyl-1,5-bis(3-(4-methylbenzyl)oxiran-2-yl)pentane-1,5-dione (**524**)



To a solution of diol **526** (120 mg, 0.31 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added sequentially NaH_2PO_4 (130 mg, 0.92 mmol) and *m*CPBA (206 mg, 0.92 mmol). The mixture was stirred vigorously for 6 h before warming to rt and stirring overnight. The reaction was quenched with sat. $NaHCO_{3(aq)}$ (15 mL) and stirred vigorously until the organic phase became clear. The phases were separated and the organic phase was washed with sat. $NaHCO_{3(aq)}$ (2 × 15 mL) and the combined aqueous phases were extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure.

To the crude residue was added CH_2Cl_2 (15 mL) and Dess-Martin Periodinane (315 mg, 0.74 mmol) and the mixture was stirred vigorously for 3 h. The reaction was quenched with sat. $NaHCO_{3(aq)}$ (15 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:Et_2O = 100:0 → 80:20) gave bis-epoxyketone **524** (31.5 mg, 24% over 2 steps, 1.5:1 d.r.) as a colourless oil.

$[\alpha]^{22}_D$: + 5 ° (*c* 0.5, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14-7.07 (m, 8H, H-3, H-4, H-18 and H-19), 3.32 (td, J_1 = 5.2 Hz, J_2 = 2.0 Hz, 1H, H-7 or H-15), 3.26 (d, J = 2.0 Hz, 1H, H-8 or H-14), 3.19-3.16 (m, 2H, H-7 or H-15 and H-8 or H-14), 2.96 (dd, J_1 = 14.1 Hz, J_2 = 4.5 Hz, 2H, H-6a and H-16a), 2.87 (dd, J_1 = 14.1 Hz, J_2 = 4.1 Hz, 2H, H-6b and H-16b), 2.55-2.44 (m, 2H, H-

10 and H-12), 2.33 (s, 6H, H-1 and H-21), 1.77 (ddd, J_1 = 13.9 Hz, J_2 = 8.9 Hz, J_3 = 5.1 Hz, 1H, H-11a), 1.56 (m, 1H, H-11b), 1.00 (d, J = 7.0 Hz, 3H, H-22 or H-23), 0.96 (d, J = 6.8 Hz, 3H, H-22 or H-23) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 210.9 (CO), 209.7 (CO), 136.8 (C), 136.7 (C), 132.9 (C), 132.7 (C), 129.5 (4 × CH), 129.1 (4 × CH), 58.8 (CH), 58.5 (CH), 58.4 (CH), 58.3 (CH), 38.6 (CH), 38.0 (CH), 37.7 (CH_2), 37.5 (CH_2), 35.1 (CH_2) 21.2 (2 × CH_3), 17.6 (CH_3), 16.9 (CH_3) ppm

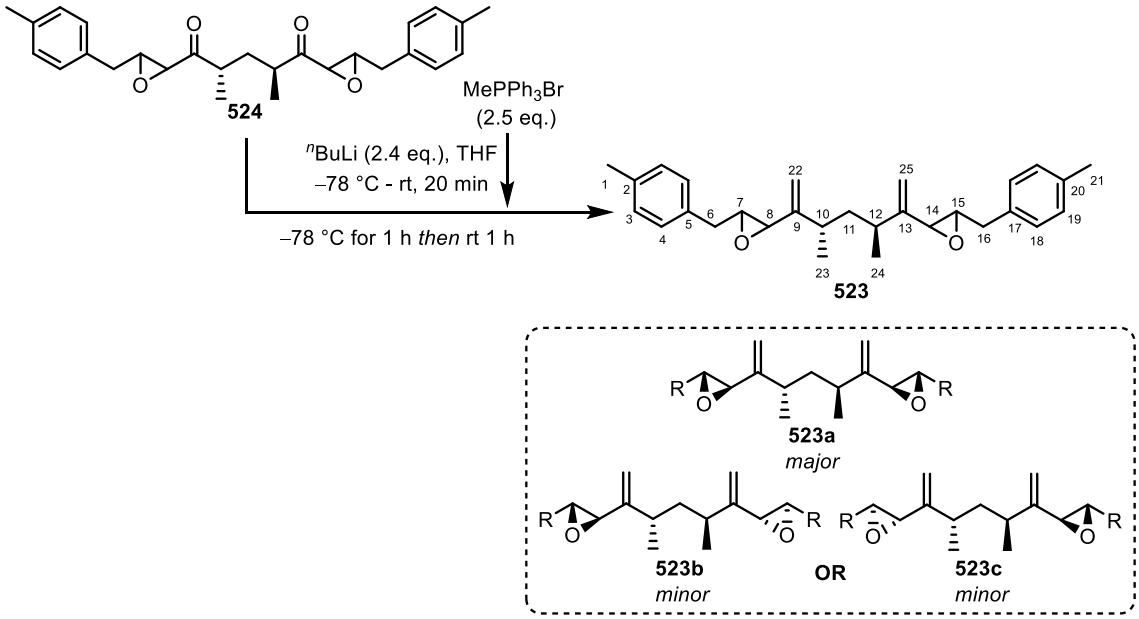
IR (neat): 2958, 2923, 1705, 1515, 1427, 803 cm^{-1}

HRMS (ESI) calculated for $C_{27}H_{36}NO_4$ $[M+NH_4]^+$: 438.2639, found 438.2633

R_f = 0.20 (Pentane:Et_2O = 80:20)

Note: NMR data shown for major diastereomer **524a** *only*

3,3'-((3*S*,5*S*)-3,5-dimethylhepta-1,6-diene-2,6-diyl)bis(2-(4-methylbenzyl)oxirane) (523)



To a solution of methyltriphenylphosphonium bromide (44.7 mg, 0.13 mmol) in THF (500 μL) at –78 °C was added ^{n}BuLi (1.6 M in hexanes, 75 μL, 0.12 mmol). The cooling bath was removed and the mixture was stirred at rt for 20 min. The solution was cooled to –78 °C and bis-epoxyketone **524** (21.0 mg, 0.05 mmol) in THF (250 μL) was added dropwise and the resulting mixture was stirred for 1 h. The cooling bath was removed and the reaction mixture was stirred at rt for 1 h. The mixture was diluted with H_2O (3 mL) and Et_2O (2 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 2 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (Pentane:Et_2O = 100:0 → 95:5) gave bis-epoxide **523** (4.6 mg, 22%, 1.5:1 d.r.) as a colourless oil.

$[\alpha]^{22}_{D}$: + 5 ° (*c* 0.25, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14-7.10 (m, 8H, H-3, H-4, H-18 and H-19), 4.98 (br. d, *J* = 4.2 Hz, 2H, H-22a and H-25a), 4.74 (br. d, *J* = 4.2 Hz, 2H, H-22b and H-25b), 3.09 (d, J_1 = 1.5 Hz, 1H, H-8 or H-14), 3.06 (d, *J* = 1.4 Hz, 1H, H-8 or H-14), 2.94-2.88 (m, 2H, H-6a and H-16a), 2.88-2.83 (m, 2H, H-7 and H-15), 2.82-2.73 (m, 2H, H-6b and H-16b), 2.33 (s, 6H, H-1 and H-21), 2.16 (m, 1H, H-10 or H-12), 2.11 (m, 1H, H-10 or H-12), 1.39 (m, 1H, H-11a), 1.33 (m, 1H, H-11b), 0.98 (d, *J* = 7.0 Hz, 3H, H-22 or H-23), 0.87 (d, *J* = 7.0 Hz, 3H, H-22 or H-23) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 149.9 (C), 149.8 (C), 136.4 (2 × C), 134.0 (2 × C), 129.4 (4 × CH), 129.0 (4 × CH), 109.4 (CH_2), 109.2 (CH_2), 61.7 (2 × CH), 58.2 (CH), 57.9 (CH), 41.5 (CH_2), 38.5 (CH_2), 38.3 (CH_2), 34.9 (CH), 34.7 (CH), 21.2 (2 × CH_3), 21.0 (CH_3), 20.4 (CH_3) ppm

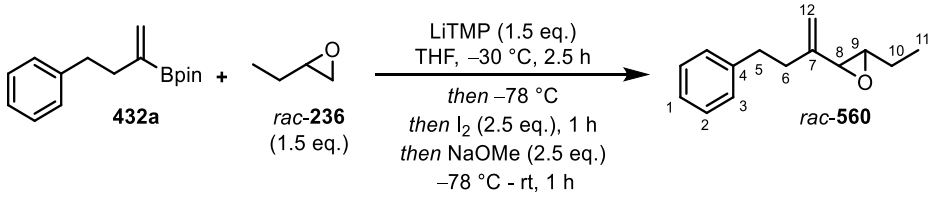
IR (neat): 2960, 2922, 1644, 1516, 1455, 904, 800 cm^{-1}

HRMS (ESI) calculated for $C_{29}H_{40}NO_2$ $[M+NH_4]^+$: 434.3054, found 434.3051

R_f = 0.60 (Pentane:Et_2O = 80:20)

Note: NMR data shown for major diastereomer **523a** *only*

2-Ethyl-3-(4-phenylbut-1-en-2-yl)oxirane *rac*-(**560**)



432a *rac*-**236** (1.5 eq.) *rac*-**560**

LiTMP (0.67 M in THF, 450 µL, 0.30 mmol) was added dropwise to a mixture of 2-ethyl oxirane *rac*-(**236**) (26 µL, 0.30 mmol) and vinyl boronic ester **432a** (51.6 mg, 0.30 mmol) in anhydrous THF (200 µL) at -30 °C, and the mixture was stirred for 2.5 h. The reaction mixture was cooled to -78 °C and I_2 (127 mg, 0.50 mmol) in anhydrous THF (500 µL) was added dropwise and the mixture was stirred for 1 h. Sodium methoxide (0.5 M in MeOH, 1.00 mL, 0.50 mmol) was added dropwise, at which point the cooling bath was removed and the reaction was stirred for 1 h at rt. The reaction was quenched with sat. $Na_2S_2O_{3(aq)}$ (2 mL) and the mixture was stirred for 20 min. CH_2Cl_2 (3 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 3 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash chromatography (Pentane:CH_2Cl_2 = 60:40) gave vinyl epoxide *rac*-**560** (26 mg, 64%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (t, *J* = 7.0 Hz, 2H, H-2), 7.21-7.17 (m, 3H, H-1 and H-3), 5.14 (br. s, 1H, H-12a), 4.95 (d, *J* = 1.4 Hz, 1H, H-12b), 3.11 (d, *J* = 2.4 Hz, 1H, H-8), 2.85-2.71 (m, 3H, H-5 and H-9), 2.37-2.21 (m, 2H, H-6), 1.64-1.56 (m, 2H, H-10), 1.01 (t, *J* = 7.6 Hz, 3H, H-11) ppm

^{13}C NMR (101 MHz, $CDCl_3$): 145.3 (C), 141.8 (C), 128.5 (4 × CH), 126.1 (CH), 112.2 (CH_2), 60.9 (CH), 60.0 (CH), 34.8 (CH_2), 33.4 (CH_2), 25.4 (CH_2), 10.0 (CH_3) ppm

IR (neat): 2958, 2934, 1496, 1455, 882, 699 cm^{-1}

HRMS (ESI) calculated for $C_{14}H_{18}ONa$: 225.1250, found 225.1243

R_f = 0.42 (Pentane:CH_2Cl_2 = 50:50)

8. References

(1) Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1956**, *78*, 5694–5695.

(2) Brown, H. C.; Singaram, B. *Pure Appl. Chem.* **1987**, *59*, 879–894.

(3) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1991**, *63*, 307–316.

(4) Zweifel, G.; Ayyangar, N. R.; Munekata, T.; Brown, H. C. *J. Am. Chem. Soc.* **1964**, *86*, 1076–1079.

(5) Sandford, C.; Aggarwal, V. K. *Chem. Commun.* **2017**, *53*, 5481–5494.

(6) Leonori, D.; Aggarwal, V. K. *Acc. Chem. Res.* **2014**, *47*, 3174–3183.

(7) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535–1551.

(8) Matteson, D. S.; Majumdar, D. *J. Organomet. Chem.* **1980**, *184*, C41–C43.

(9) Matteson, D. S.; Mah, R. W. H. *J. Am. Chem. Soc.* **1963**, *85*, 2599–2603

(10) Rathke, M. W.; Chao, E.; Wu, G. *J. Organomet. Chem.* **1976**, *122*, 145–149.

(11) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7588–7590.

(12) Bottoni, A.; Lombardo, M.; Neri, A.; Trombini, C. *J. Org. Chem.* **2003**, *68*, 3397–3405.

(13) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590–7591.

(14) Matteson, D. S. *Acc. Chem. Res.* **1988**, *21*, 294–300.

(15) Matteson, D. S.; Jesthi, P. K.; Sadhu, K. M. *Organometallics* **1984**, *3*, 1284–1288.

(16) Matteson, D. S.; Erdik, E. *Organometallics* **1983**, *2*, 1083–1088.

(17) Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077–2078.

(18) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron: Asymmetry* **1997**, *8*, 3711–3713.

(19) Hoffmann, R. W.; Landmann, B. *Angew. Chem. Int. Ed.* **1984**, *96*, 427–428.

(20) Matteson, D. S.; Beedle, E. C. *Tetrahedron Lett.* **1987**, *28*, 4499–4502.

(21) Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 810–819.

(22) Man, H.-W.; Matteson, D. S. *J. Org. Chem.* **1996**, *61*, 6047–6051.

(23) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem. Int. Ed.* **1990**, *29*, 1422–1424.

(24) Al-Aseer, M.; Beak, P.; Hay, D.; Kempf, D. J.; Mills, S.; Smith, S. G. *J. Am. Chem. Soc.* **1983**, *105*, 2080–2082.

(25) Würthwein, E.-U.; Hoppe, D. *J. Org. Chem.* **2005**, *70*, 4443–4451.

(26) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870–11871.

(27) Zeng, W.; Fröhlich, R.; Hoppe, D. *Tetrahedron* **2005**, *61*, 3281–3287.

(28) Schlosser, M.; Stähle, M. *Angew. Chem. Int. Ed.* **2006**, *94*, 142–143.

(29) Hoppe, D.; Krämer, T. *Angew. Chem. Int. Ed.* **1986**, *25*, 160–162.

(30) Hoppe, D. *Angew. Chem. Int. Ed.* **1984**, *23*, 932–948.

(31) Hine, J.; Skoglund, M. J. *J. Org. Chem.* **1982**, *47*, 4766–4770.

(32) Hoppe, D.; Kramer, T.; Schwark, J.-R.; Zschage, O. *Pure Appl. Chem.* **1990**, *62*, 1999–2006.

(33) Zschage, O.; Schwark, J.-R.; Krämer, T.; Hoppe, D. *Tetrahedron* **1992**, *48*, 8377–8388.

(34) Becker, J.; Fröhlich, R.; Salorinne, K.; Hoppe, D. *Chem. Eur. J.* **2007**, *2007*, 3337–3348.

(35) Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed.* **1997**, *36*, 2282–2316.

(36) Beckmann, E.; Hoppe, D. *Synthesis* **2005**, 217–222.

(37) Beckmann, E.; Desai, V.; Hoppe, D. *Synlett* **2004**, 2275–2280.

(38) Kocienski, P. J.; Dixon, N. *Synlett* **1989**, 52–54.

(39) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 7491–7494.

(40) Leonori D., Aggarwal V.K. (2015) *Reagent-Controlled Lithiation–Borylation.* In: Fernández E., Whiting A. (eds) Synthesis and Application of Organoboron Compounds. Topics in Organometallic Chemistry, vol 49. Springer, Switzerland

(41) Besong, G.; Jarowicki, K.; Kocienski, P. J.; Sliwinski, E.; Boyle, F. T. *Org. Biomol. Chem.* **2006**, *4*, 2193–2207.

(42) Matteson, D. S.; Hurst, G. D. *Heteroat. Chem.* **1990**, *1*, 65–74.

(43) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778–782.

(44) Larouche-Gauthier, R.; Fletcher, C. J.; Couto, I.; Aggarwal, V. K. *Chem. Commun.* **2011**, *47*, 12592.

(45) Leonori, D.; Aggarwal, V. K. *Acc. Chem. Res.* **2014**, *47*, 3174–3183.

(46) Noble, A.; Roesner, S.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2016**, *55*, 15920–15924.

(47) Varela, A.; Garve, L. K. B.; Leonori, D.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 2127–2131.

(48) Burns, M.; Essafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey, J. N.; Aggarwal, V. K. *Nature* **2014**, *513*, 183–188.

(49) Bootwicha, T.; Feilner, J. M.; Myers, E. L.; Aggarwal, V. K. *Nat. Chem.* **2017**, *9*, 896–902.

(50) Harrison, P. W. B.; Kenyon, J.; Phillips, H. *J. Chem. Soc.* **1926**, 2079–2090.

(51) Annunziata, M.; Capozzi, M.; Cardellicchio, C.; Naso, F.; Tortorella, P. *J. Org. Chem.* **2000**, *65*, 2843–2846.

(52) Durst, T.; Lebelle, M. J.; Van Den Elzen, R.; Tin, K.-C. *Can. J. Chem.* **1974**, *52*, 761–766.

(53) Jacobus, J.; Mislow, K. *J. Am. Chem. Soc.* **1967**, *89*, 5228–5234.

(54) Wolf, C. *Dynamic Stereochemistry of Chiral Compounds : Principles and Applications*; RSC Pub, **2008**, Chapter 2, 6–28.

(55) Annunziata, M.; Capozzi, M.; Cardellicchio, C.; Naso, F.; Rosito, V. *J. Org. Chem.* **2002**, *67*, 7289–7294.

(56) Hoffmann, R. W.; Nell, P. G. *Angew. Chem. Int. Ed.* **1999**, *38*, 338–340.

(57) Hoffmann, R. W.; Nell, P. G.; Leo, R.; Harms, K. *Chem. Eur. J.* **2000**, *6*, 3359–3365.

(58) Satoh, T.; Takano, K.; Ota, H.; Someya, H.; Matsuda, K.; Koyama, M. *Tetrahedron* **1998**, *54*, 5557–5574.

(59) Hoffmann, R. W. *Chem. Soc. Rev.* **2003**, *32*, 225–230.

(60) Hoffmann, R. W.; Hölzer, B.; Knopff, O.; Harms, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 3072–3074.

(61) Hoffmann, R. W.; Hölzer, B. *Chem. Commun.* **2001**, *5*, 491–492.

(62) Blakemore, P. R.; Marsden, S. P.; Vater, H. D. *Org. Lett.* **2006**, *8*, 773–776.

(63) Gessner, V. H. *Chem. Commun.* **2016**, *52*, 12011–12023.

(64) Hofmann, R. W.; Julius, M.; Chemla, F.; Ruhland, T.; Frenzen, G. *Tetrahedron* **1994**, *50*, 6049–6060.

(65) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: New York, **2002**.

(66) Blakemore, P. R.; Burge, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3068–3069.

(67) Soundararajan, R.; Li, G.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 8957–8960.

(68) Negishi, E. *Dalton Trans.* **2005**, 827–848.

(69) Rayner, P. J.; O'Brien, P.; Horan, R. A. J. *J. Am. Chem. Soc.* **2013**, *135*, 8071–8077.

(70) Balieu, S.; Hallett, G. E.; Burns, M.; Bootwicha, T.; Studley, J.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2015**, *137*, 4398–4403.

(71) Ritter, S. K. *Chem. Eng. News* **2017**, *95*, 18–20.

(72) Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3130–3136.

(73) Bolm, C.; Bienewald, F. *Angew. Chem. Int. Ed.* **1996**, *34*, 2640–2642.

(74) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011–8019.

(75) Blakemore, P. R.; Burge, M. S.; Sephton, M. A. *Tetrahedron Lett.* **2007**, *48*, 3999–4002.

(76) Emerson, C. R.; Zakharov, L. N.; Blakemore, P. R. *Chem. Eur. J.* **2013**, *19*, 16342–16356.

(77) Pulis, A. P.; Blair, D. J.; Torres, E.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 16054–16057.

(78) Emerson, C. R.; Zakharov, L. N.; Blakemore, P. R. *Org. Lett.* **2011**, *13*, 1318–1321.

(79) Satoh, T.; Matsue, R.; Fujii, T.; Morikawa, S. *Tetrahedron* **2001**, *57*, 3891–3898.

(80) Beak, P.; McKinnie, B. G. *J. Am. Chem. Soc.* **1977**, *99*, 5213–5213.

(81) Gessner, V. H.; *Chem. Commun.* **2016**, *52*, 12011–12023.

(82) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958–2961.

(83) Zhang, P.; Gawley, R. E. *J. Org. Chem.* **1993**, *58*, 3223–3224.

(84) Durst, T.; Viau, R.; McClory, M. R. *J. Am. Chem. Soc.* **1971**, *93*, 3077–3078.

(85) Nakamura, S.; Takemoto, H.; Ueno, Y.; Toru, T.; Kakumoto, T.; Hagiwara, T. *J. Org. Chem.* **1999**, *2000*, 469–474.

(86) Marsch, M.; Massa, W.; Baum, G.; Boche, G.; Harms, K. *Angew. Chem. Int. Ed.* **1986**, *25*, 1011–1012.

(87) Matoušek, V.; Togni, A.; Bizet, V.; Cahard, D. *Org. Lett.* **2011**, *13*, 5762–5765.

(88) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156–2164.

(89) Prieto, A.; Baudoin, O.; Bouyssi, D.; Monteiro, N. *Chem. Commun.* **2016**, *52*, 869–881.

(90) Blanc, R.; Groll, K.; Bernhardt, S.; Stockmann, P.; Knochel, P. *Synthesis* **2014**,

46, 1052–1058.

(91) Whitesides, G. M.; Fischer, W. F.; San Filippo, J.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871–4882.

(92) Lipshutz, B. H.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 4696–4698.

(93) Sun, X.; Blakemore, P. R. *Org. Lett.* **2013**, *15*, 4500–4503.

(94) Wood, M. E.; Bissiriou, S.; Lowe, C.; Windeatt, K. M. *Org. Biomol. Chem.* **2013**, *11*, 2712–2723.

(95) Satoh, T. *Chem. Rev.* **1996**, 96, 3303–3325.

(96) Crandall, J. K.; Lin, L. C. *J. Am. Chem. Soc.* **1967**, *89*, 4526–4527.

(97) Eisch, J. J.; Galle, J. E. *J. Organomet. Chem.* **1988**, *341*, 293–313.

(98) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, *55*, 4835–4840.

(99) Florio, S.; Capriati, V.; Di Martino, S. *Tetrahedron Lett.* **1998**, *39*, 5639–5642.

(100) Florio, S.; Capriati, V.; Di Martino, Abbotto A. *Eur. J. Org. Chem.* **1999**, 409–417.

(101) Yoshihiro Y.; Toshimasa K. A.; Uneyama, K. *Org. Lett.* **2001**, *4*, 173–176.

(102) Zhang, H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 11590–11594.

(103) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.

(104) Lohse, P.; Loner, H.; Acklin, P.; Sternfeld, F.; Pfaltz, A. *Tetrahedron Lett.* **1991**, *32*, 615–618.

(105) Satoh, T.; Horiguchi, K. *Tetrahedron Lett.* **1995**, *36*, 8235–8238.

(106) Satoh, T.; Kobayashi, S.; Nakanishi, S.; Horiguchi, K.; Irisa, S. *Tetrahedron* **1999**, *55*, 2515–2528.

(107) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625–1642.

(108) Hodgson, D. M.; Norsikian, S. L. M. *Org. Lett.* **2001**, *3*, 461–463.

(109) Hodgson, D. M.; Reynolds, N. J.; Coote, S. J. *Tetrahedron. Lett.* **2002**, *43*, 7895–7897.

(110) Vedrenne, E.; Wallner, O. A.; Vitale, M.; Schmidt, F.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 165–168.

(111) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380–416.

(112) Fawcett, A.; Nitsch, D.; Ali, M.; Bateman, J. M.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2016**, *55*, 14663–14667.

(113) Pulis A. A.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2012**, *134*, 7570–7574.

(114) Bojaryn, K.; Fritsch, S.; Hirschhaüser, C. *Org. Lett.* **2019**, *21*, 2218–2222.

(115) Prileschajew, N. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 4811−4815.

(116) Fuentespina R. R.; de la Cruz, J. A. G.; Durin, G.; Mamane V.; Weibel, J-M.; Pale, P. *Beilstein J. Org. Chem.* **2019**, *15*, 1416−1424.

(117) Fawcett, A. *Unpublished Results*, Second Year Report, University of Bristol, **2017**.

(118) ten Brink, G. J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4104–4124

(119) Armstrong, R. J.; Aggarwal, V. K. *Org. Synth.* **2017**, *94*, 234–251.

(120) Chen, J. L. Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2014**, *53*, 10992–10996.

(121) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, J. R. *Vogel's Textbook of Practical Organic Chemistry (5th Ed)*, Wiley & Sons, New York, **1991**.

(122) Carreras, J.; Caballero, A.; Pérez, P. J. *Chem. Asian. J.* **2019**, *14*, 329−343.

(123) Miyaura, N.; Suzuki, A. *Chem.* Rev. **1995**, *95*, 2457−2483.

(124) Miyaura, N.; Satoh, M.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 3745−3748.

(125) Thomas, A. A.; Denmark, S. E. *Science* **2016**, *352*, 329−333.

(126) Sittihan, S.; Jamison, T. F. *J. Am. Chem. Soc.* **2019**, *141*, 11239−11244.

(127) Brown, D. G.; Boström, J. *J. Med. Chem.* **2016**, *59*, 4443−4458.

(128) Chan, D. M. T.; Monaco, K. L.; Wang, R-P.; Winters, M. P. *Tetrahedron Lett.***1998**, *39*, 2933–2936.

(129) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.***1998**, *39*, 2941–2944.

(130) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927–4931.

(131) Shade, R. E.; Hyde, A. M.; Olsen, J-C.; Merlic, C. A. *J. Am. Chem. Soc.* **2010**, *132*, 1202–1203.

(132) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131.

(133) Ganić, A.; Pfaltz, A. *Chem. Eur. J.* **2012**, *18*, 6724–6728.

(134) Nishikawa, D.; Hirano, K.; Miura, M. *J. Am. Chem.* Soc. **2015**, *137*, 15620–15623.

(135) Lee, J.; Torker, S.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 821–826.

(136) Syzmaniak, A. A.; Zhang, C.; Coombs, J. R.; Morken, J. P. *ACS. Catal.* **2018**, *8*, 2897–2901.

(137) Ohmura, T. Taniguchi, H.; Kondo, Y.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 3518–3519.

(138) Yeung, K.; Talbot, F. J. T.; Howell, G. P.; Pulis, A. P.; Procter, D. J. *ACS. Catal.* **2019**, *9*, 1655–1661.

(139) Hussain, M. M.; Toribio, J. H.; Carroll, P. J.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 6337–6340.

(140) Chan, J-L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2014**, *53*, 10992–10996.

(141) Coombs, J. R.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 16140–16143.

(142) Zweifel, G.; Arzoumanian, H.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 3652–3653.

(143) Armstrong, R. J.; Aggarwal, V. K. *Synthesis*, **2017**, *49*, 3323–3336.

(144) Armstrong, R. J.; García-Ruiz, C.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 786–790.

(145) Tao, Z.; Robb, K. A.; Panger, J. L.; Denmark, S. E. *J. Am. Chem. Soc.* **2018**, 140, 15621–15625.

(146) Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Syzmaniak, A. A.; Chierchia, M. P.; Morken J. P. *Science* **2016**, *351*, 70–74.

(147) Kishkewitz, M.; Okamoto, K.; Mück-Lichtenfeld, C.; Studer, A. *Science* **2017**, *355*, 936–937.

(148) Silvi, M.; Sandford, C. Aggarwal, V. K. *J. Am. Chem. Soc.* **2017**, *139*, 5736–5739.

(149) Chierchia, M.; Xu, P.; Lovinger, G. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2019**, *58*, 14245–14249.

(150) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370–4371.

(151) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482–3485.

(152) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127–3128.

(153) Pereira, S.; Srebnik, M. *Tetrahedron Lett.* **1996**, *37*, 3283–3286.

(154) Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 6026–6029.

(155) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001–8006.

(156) Coombs, J. R.; Zhang, L.; Morken, J. P. *Org. Lett.* **2015**, *17*, 1708–1711.

(157) Bassindale, A. R.; Ellis, R. J.; Lau, J. C-Y., Taylor, P. G. *J. Chem. Soc. Chem. Commun*. **1986**, 98–100.

(158) Namirembe, S.; Gao, C.; Wexler, R. P.; Morken, J. P. *Org. Lett.* **2019**, *21*, 4392–4394.

(159) Kolonko, K. J.; Biddle, M. M.; Guzei, I. A.; Reich, H. J. *J. Am. Chem. Soc.* **2009**, *131*, 11525–11534.

(160) Murray, S. A.; Luc, E. C. M.; Meek, S. J. *Org. Lett.* **2018**, *20*, 469-472.

(161) Li, C.; Wang, J.; Barton, L. M.; Yu, S.; Tian, M.; Peters, D. S.; Kumar, M.; Yu, A. W.; Johnson, K. A.; Chatterjee, A. K.; Yan, M.; Baran, P. S. *Science* **2017**, *356*, eaam7355.

(162) Wu, J., He, L.; Noble, A.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2018**, *140*, 10700–107004.

(163) Friese, F. W.; Studer, A. *Angew. Chem. Int. Ed.* **2019**, *58*, 9561–9564.

(164) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752–6756.

(165) Brown, H. C.; Imai, T.; Bhat, N. G. *J. Org. Chem.* **1986**, *51*, 5277−5282.

(166) Chan, T-H. *Acc. Chem. Res.* **1977**, *10*, 442−448.

(167) Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 230−236.

(168) Shimizu, M.; Fujimoto, T.; Minezaki, H.; Hata, T.; Hiyama, T. *J. Am. Chem. Soc*. **2001**, *123*, 6947−6948.

(169) Aparece, M. D.; Gao, C.; Lovinger, G. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2019**, *58*, 592−595.

(170) Cheng, M-J.; Tsai, I-L.; Lee, S-J.; Jayaprakasam, B.; Chen, I-S. *Phytochemistry* **2005**, *66*, 1180−1185.

(171) Stierle, D. B.; Stierle, A. A.; Loewen G. *J. Nat. Prod.* **1998**, *61*, 251−252.

(172) Schmidt, Y.; Lehr, K.; Colas, L.; Breidt, B. *Chem. Eur. J.* **2012**, *18*, 7071−7081.

(173) Stahl, M.; Schopfer, U.; Frenking, G.; Hoffmann, R. W. *J. Org. Chem.* **1996**, *61*, 8083−8088.

(174) Blair, D. J.; Tanini, D.; Bateman, J. M.; Scott, H. K.; Myers, E. L.; Aggarwal, V. K. *Chem. Sci.* **2017**, *8*, 2898−2903.

(175) Krätzschmar, F.; Kaßel, M.; Delony, D.; Breder, A. *Chem. Eur. J.* **2015**, *21*, 7030−7034.

(176) Ortar, G. *Tetrahedron* **2003**, *44*, 4311−4314.

(177) Marcone, J. E.; Moloy, K. G. *J. Am. Chem. Soc*. **1998**, *120*, 8527−8528.

(178) Amatore, C.; Jutand, A.; Thuilliez, A. *Organometallics* **2001**, *20*, 3241−3249.

(179) Van Leeuwen, P. W, M. N.; Kamer, P. C. J.; Reek, J. N. H. *Pure Appl. Chem.* **1999**, *71*, 1443−1452.

(180) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008,** *108*, 3958–3987.

(181) Wang, Z-X.; Tu, Y.; Frohn, M.; Zhang, J-R.; Shi, Y. *J. Am. Chem. Soc.* **1997,** *119*, 11224–11235.

(182) Jenson, C.; Liu, J.; Houk, K. N.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1997**, *119*,

12982–12983.

(183) Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213–5218.

(184) Kolb, H. C.; VanNieuwenzhe, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(185) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278–1291.

(186) Zhang, W.; Carter, R. G. *Org. Lett.* **2005**, *7*, 4209–4212.

(187) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515–10530.

(188) Zhang, H.; Ma, S.; Yuan, Z.; Chen, P.; Xie, X.; Wang, X.; She, X. *Org. Lett.* **2017**, *19*, 3478–3481.

(189) Batory, L. A.; McInnis, C. E.; Njardarson, J. T. *J. Am. Chem. Soc.* **2006**, *128*, 16054–16055.

(190) Ghosh, A. K.; Thompson, W. J.; Holloway, M. K.; McKee, S. P.; Duong, T. T.; Lee, H. Y.; Munson, P. M.; Smith, A. M.; Wai, J. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem*. **1993**, *36*, 2300–2310.

(191) Lifchits, O.; Mahlau, M.; Reisinger, C. M.; Lee, A.; Farès, C.; Polyak, I.; Gopakumar, G.; Thiel, W.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 6677–6693.

(192) Hehre, W. J. *A Guide to Molecular Mechanics and Quantum Chemical Calculations*; Wavefunction, Inc.: Irvine, USA, **2003**.

(193) Young, D. *Computational Chemistry: A Practical Guide for Applying Techniques to Real World Problems*; John Wiley & Sons, Inc.: Canada, **2001**.

(194) Wu, J.; Lorenzo, P.; Zhong, S.; Ali, M.; Butts, C. P.; Myers, E. L.; Aggarwal, V. K. *Nature* **2017**, *547*, 436–440.

(195) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096–17098.

(196) Burchat, A. F.; Chong, J. M.; Nielsen. N. *J. Organomet. Chem.* **1997**, *542*, 281–283.

(197) Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *8*90–891.

(198) O'Mahony, G. E.; Ford, A.; Maguire, A. R. *J. Org. Chem.* **2012**, *77*, 3288–3296.

(199) Mykura, R. C.; Veth, S.; Varela, A.; Dewis, L.; Farndon, J.; Myers, E. L.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2018**, *140*, 14677–14678.

(200) Yamamoto, Y.; Fujikawa, R.; Umemoto, T.; Miyaura, N. *Tetrahedron* **2004**, *60*, 10695–10700.

(201) Fawcett, A.; Pradeilles, J.; Wang, Y.; Mutsuga, T.; Myers, E. L.; Aggarwal, V. K. *Science*, **2017**, *357*, 283–286.

(202) Aichhorn, S.; Bigler, R.; Myers, E. L.; Aggarwal, V. K.; *J. Am. Chem. Soc.* **2017**, *139*, 9519–9522.

(203) Fawcett, A.; Biberger, T.; Aggarwal, V. K. *Nat. Chem.* **2019**, *11*, 117–122.

(204) Fawcett, A.; Murtaza, A.; Gregson, C. H. U.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2019**, *141*, 4573–4578.

(205) Brondani, P. B.; Dudek, H.; Reis, J. S.; Fraaije, M. W.; Andrade, L. H. *Tetrahedron:Asymmetry* **2012**, *23*, 703–708.

(206) Ito, I.; Kubota, K. *Org. Lett.* **2012**, *14*, 890–893.

(207) Wilson, C. M.; Ganesh, V.; Noble, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 16318–16322.

(208) Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5359–5363.

(209) Craig, S.; Gao, L.; Lee, I.; Gray, T.; Berdis, A. J. *J. Med. Chem.* **2012**, *55*, 2437–2451.

(210) Casoni, G.; Myers, E. L.; Aggarwal, V. K. *Synthesis* **2016**, *48*, 3241–3253.

(211) Hickmann, V.; Alcarazo, M.; Fürstner A. *J. Am. Chem. Soc.* **2010**, *132*, 11042–1044.

(212) Perry, R. J.; Lewis, L. N.; O'Brien, M. J.; Soloveichek, G. L.; Kniajanski, S.; Lam, T. H.; Lee, J. L.; Rubinsztajn, M. I. (**2011**) *Carbon Dioxide Absorbent and Method Of Using The Same*, WO014273 (A1).

(213) Guan, W.; Michael, A. K.; McIntosh, M. L.; Koren-Selfridge, L.; Scott, J. P.; Clark, T. B. *J. Org. Chem.* **2014**, *79*, 7199–7204.

(214) Seo, H.; Liu, A.; Jamison, T. F. *J. Am. Chem. Soc.* **2017**, *139*, 13969–13972.

(215) Su, Y.; Li, Q.; Zhao, Y.; Gu, P. *Org. Lett.* **2016**, *18*, 4356–4359.

(216) Zhang, P.; Suárez, J. M.; Driant, T.; Derat, E.; Zhang, Y.; Ménand, M.; Roland, S.; Sollogoub, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 10821–10825.

(217) Ni, Z.; Yang, P.; Ng, D. K. P. G.; Tzeng, Y.; Lull, T. *J. Am. Chem. Soc.* **1990**, *112*, 9356–9364.

(218) Fukuda, K.; Miyashita, M.; Tanino, K. *Tetrahedron Lett.* **2010**, *51*, 4523–4525.

(219) Lühning, L. H.; Rosien, M.; Doye, S. *Synlett* **2017**, *28*, 2489–2494.

(220) Fan, Q.; Yeung, C.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 4041–4045.

(221) Grundke, G.; Hoffmann, H. M. R. *J. Org. Chem.* **1981**, *46*, 5428–5431.

(222) Miura, T.; Takahashi, Y.; Murakami, M. *Chem. Commun.* **2007**, 595–97.